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A CRITICAL APPRAISAL OF ORAL HYPOGLYCEMIC AGENTS*

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In a recent symposium on orally effective hypoglycemic agents (1) several participants remarked, "these drugs are here to stay." Back of such an opinion stands the obvious desire of every diabetic to avoid daily or more frequent injections of insulin. Insulin is the logical substitution therapy for the diabetic, for it is "physiologically antidiabetic." Therefore, a heavy burden falls upon investigators, particularly upon those charged with human trials, to make sure that any orally active hypoglycemic or antidiabetic agent is physiologically applicable, potent and safe.

In what ways do the presently available hypoglycemic agents fulfill these requirements? Although many facets of this question remain wholly unanswered, the very fact that powerful blood sugar-lowering agents have been discovered has provided a great stimulus for research into the mechanisms underlying the faulty metabolism of diabetes mellitus.

CHEMISTRY

Two chemically different types of hypoglycemic compounds have come to clinical trial—the sulfonylureas and the guanidine derivatives. The structural formulas of 4 compounds of the sulfonylurea group are represented in Figure 1, and 2 compounds of the guanidine group in Figure 2. The only chemical arrangement which these two types of compound have in common is $-HN-\overset{\displaystyle R}{\overset{|}{C}}-NH-$ (where R is an O or an NH). In the guanidine derivatives R is an NH and in the sulfonylureas it is an O. Common to the members of the sulfonylurea group is the bivalent sulfonylamide radical, $-NH-SO_2-$, to one valence of which a benzene ring is attached.

* The studies on metahexamide referred to in this paper were aided by funds from the Clinical Studies Division, Research Service, Veterans Administration, Washington, D. C. through a V.A. Cooperative Diabetes Study.

PHYSIOLOGIC CONSIDERATIONS

The 6 preparations, the chemical formulas of which are shown in Figures 1 and 2, have been or are being tried extensively in the treatment of diabetes mellitus by investigators in this country and abroad. How physiologically applicable are they? In comparing their action with that of insulin, the concepts of Stetten (2, 3) and of Stadie (4) regarding the point or points of action of insulin have been heavily drawn upon, and Figure 3 is based upon one of Stetten's schemata (3). One of the functions, if not the only function of insulin is to further the transport of glucose across cellular membranes, thus making this substance available for reaction with intracellular constituents. In the second place, insulin has been shown to enhance the activity of hexokinase in transferring glucose into glucose-6-phosphate in the presence of adenosine triphosphate (ATP). Whether insulin acts solely on the transport mechanism or the enzyme mecha-

ORAL HYPOGLYCEMIC SULFONYLUREAS

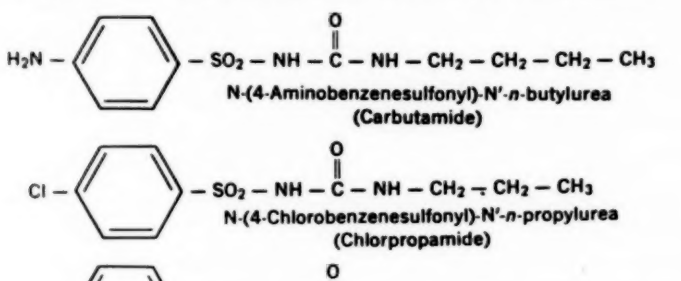
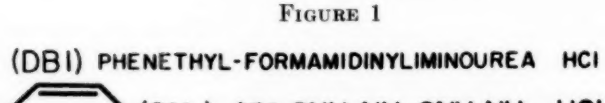

H2N – – SO2 – NH – C – NH – CH2 – CH2 – CH2 – CH3
O
N-(4-Aminobenzenesulfonyl)-N'-n-butylurea
(Carbutamide)
Cl – – SO2 – NH – C – NH – CH2 – CH2 – CH3
O
N-(4-Chlorobenzenesulfonyl)-N'-n-propylurea
(Chlorpropamide)
H3C – – SO2 – NH – C – NH – CH2 – CH2 – CH2 – CH3
O
N-(4-Methylbenzenesulfonyl)-N'-butylurea
(Tolbutamide)
H3C – – SO2 – NH – C – NH –
O
H
H2N
N-(3-Amino-4-methylbenzenesulfonyl)-N'-cyclohexylurea
(Metahexamide)

FIGURE 1



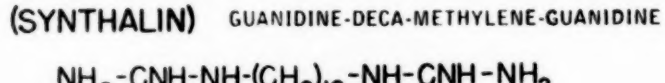


FIGURE 2

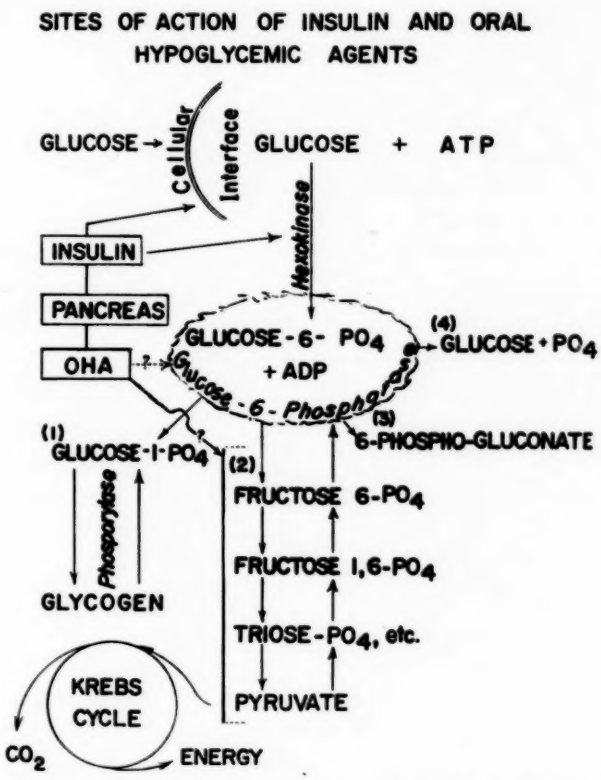


FIG. 3. Possible sites of action of oral hypoglycemic agents. Solid lines represent a stimulation of furtherance of the indicated action, and dotted lines represent an inhibition. ATP=adenosine triphosphate; OHA=oral hypoglycemic agent. OHA may further the production and/or release of insulin by the pancreas or in some way alter pancreatic function to improve the intermediary metabolism of food stuffs. This is not the only action. Glucose-6-phosphatase may be inhibited but, *in vitro*, the concentrations of OHA necessary for this action are greater than those assumed to occur *in vivo*. It has been suggested that these drugs increase anaerobic glycolysis, particularly at the pyruvate-lactic acid stages. None of the hypotheses so far advanced adequately explains all of the facts. It is clear, however, that the release of glucose by the liver is decreased through the action of OHA. (Based upon data from Stetten (3).)

nism or on both is not clearly established, but there is no doubt that its presence favors the formation of intracellular glucose-6-phosphate from extracellular glucose. According to Stetten (3) the glucose-6-phosphate thus formed may have one of several fates, all of which are initiated by the action of glucose-6-phosphatase:

"1. Transformation to glucose-1-phosphate from which glycogen and other glucosides arise.

"2. Rearrangement to fructose-6-phosphate, which, after further phosphorylation to fructose-1,6-diphosphate, may proceed over the steps outlined by Embden, Meyerhof and others to pyruvic and lactic acids. This process serves, in the animal, as the main source of fuel for the all-important citric acid cycle, the major energy-yielding process in the body.

"3. Hydrolysis, by an appropriate glucose-6-phosphatase to glucose and inorganic phosphate. This enzyme has been demonstrated in liver and presumably occurs in kidney and intestinal mucosa but is absent from muscle.

"4. Oxidation to 6-phosphogluconic acid which serves as precursor for the important pentose, ribose, of nucleic acids and initiates a pathway of oxidation currently referred to as the 'hexosemonophosphate shunt.' "

In insulin deficiency, there is a failure of, or deficiency in the formation of glucose-6-phosphate. Therefore the synthesis of glycogen, particularly in muscle, is decreased or inhibited; the rises in the blood lactate level and respiratory quotient which follow the injection of glucose into a normal animal, fail to occur.

From Figure 3 it can be seen that when insulin is administered to a normal subject, a series of reactions occur which tend to remove glucose from the blood and utilize it in the liver and peripheral tissues. Glycogen is formed from glucose in both liver and muscle, particularly the latter. By way of the Embden-Meyerhof or conventional pathway, the breakdown of glucose to pyruvic and lactic acids is furthered. Lipogenesis and protein synthesis are increased. The oxidation of glucose to carbon dioxide and water is enhanced. By way of the hexosemonophosphate shunt, protein synthesis is favored through the formation of the pentose, ribose, which takes part in the synthesis of nucleic acids.

When there is a deficiency of insulin, as in the diabetic animal, the utilization of glucose by liver and muscle is decreased. Therefore, the concentration of blood glucose rises, glycogen stores are diminished, and lactate production decreases.

In the schema depicted in Figure 3, it has been proposed that the sulfonylureas may act to stimulate the beta cells of the pancreatic islands of Langerhans to secrete or release insulin, thereby furthering all of the reactions into which insulin normally enters. On the other hand, there are those who believe that the oral hypoglycemic drugs may act upon the liver directly to reduce the utilization of glucose through inhibition of the enzyme, glucose-6-phosphatase or, more likely, some other enzyme system. There is some evidence to show that phenethyl diguanide may act by increasing anaerobic glycolysis, that is, by furthering the events of the Embden-Meyerhof pathway or cycle (5).

Which, if any, of the processes normally influenced by insulin are involved in the action of the oral hypoglycemic agents? To date at least 5 theories have been propounded to explain the actions of these substances:

1. *Insulin-simulating action.* Both insulin and the oral hypoglycemic agents produce hypoglycemia. One group of workers have found that not only blood sugar, but also blood lactic acid, pyruvate, alpha-ketoglutaric acid, ketones and acetone and serum inorganic phosphorus and citric acid following fasting and a test meal responded identically to the administration of insulin or chlorpropamide (6). Intravenously administered tolbutamide has also been shown "to produce hypoglycemic effects comparable to those of insulin" (7). However, in correspondingly effective hypoglycemic doses, the removal of administered glucose is more rapid with insulin than with the sulfonylureas (8, 9). Furthermore, under the influence of the latter compounds, the majority of workers have found no increase in the production of glucose by the liver (9–20), but this has also been

denied (21, 22). The liver does not seem to retain potassium and phosphate following the use of tolbutamide as it does in the earlier stages of the action of insulin (9), although following intravenous injection a fall in the level of serum phosphate has been reported (7). An increase in labelled carbon dioxide from fed glucose has been both affirmed (15) and denied (12, 23). In the normal fasted animal, insulin has little or no influence upon the incorporation of administered glucose into hepatic glycogen (9), whereas tolbutamide markedly increases the turnover without influencing the total amount present (9). The conversion of hepatic glycogen to glucose is decreased if large amounts of tolbutamide are present (24).

In peripheral tissues, most workers have found that the sulfonylureas have little or no influence upon the uptake of glucose or the formation of glycogen (16, 23, 25, 26), but others have demonstrated an increase in the formation of glycogen, appearing later and significantly less pronounced than following administration of insulin (9, 27, 28). Still others have observed a significant A-V glucose difference (22). Both insulin and tolbutamide increase the incorporation of C^{14} into hepatic fatty acids, but only the former increases peripheral fatty acid activity (9, 29).

Insulin and chlorpropamide similarly decrease hepatic glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase (30).

From the foregoing, it seems unlikely that the sulfonylureas act similarly to insulin or through the same processes as insulin.

2. *Effect on alpha cells of the pancreatic islets.* Levine (16) called attention to the fact that the earlier demonstration of histologic changes in the alpha cells following the administration of the sulfonylureas had not been confirmed by subsequent workers. He further commented upon the fact that the "alpha cell depression hypothesis cannot account for the rapid hypoglycemia which follows the administration of these drugs" (15).

3. *Inhibition of insulinase.* Insulinase activity has been depressed by the arylsulfonylureas (31–33), but the amounts necessary have been much larger than those required to elicit the hypoglycemic responses to these substances (34). Moreover, neither the specificity of this proteolytic enzyme for the insulin molecule nor its role in normally regulating the amount of insulin available to peripheral tissues has been definitely demonstrated (15).

4. *Diminution in the release and/or production of glucose by the liver.* The mechanisms which may be concerned here have already been touched upon in dealing with the insulin-simulating action of the oral hypoglycemic compounds. The evidence for a diminished output of glucose by the liver under the influence of both the arylsulfonylureas (11–14, 16, 17, 35) and the diguanides (5) is fairly convincing. It has been suggested that the action of the sulfonylureas is due to a blocking of the normal hepatic response to epinephrine (9), as the accelerated glycogenolysis induced by epinephrine *in vitro* can be diminished or prevented by the presence of tolbutamide. That tolbutamide and carbutamide can inhibit the action of glucose-6-phosphatase has been demonstrated (36, 37); however, the concentrations necessary are much higher than those required to produce the

hypoglycemic effects. The action of the diguanidines is thought by Williams and his associates to be one of furthering anaerobic glycolysis in both the liver and the periphery (5).

When all of the evidence is considered it would appear likely that one of the avenues of action of the sulfonylureas is an inhibition of some one or more of the steps concerned with the production of glucose by the liver. Levine comments: "This is an extremely important issue to settle because any drug which chronically affects the set of systems in the liver, which manufacture and release glucose, would ultimately be expected to produce functional and perhaps anatomical damage to the liver" (15).

5. *Pancreatotropic action.* There seems to be a general feeling that the pancreatotropic hypothesis regarding the action of the arylsulfonylureas is well supported (38, lit. cit; 39), but this is certainly not the only mechanism of action (9, 11, 14, 15, 17). Favoring such a type of activity are the following:

(a) No hypoglycemic activity can be demonstrated for the arylsulfonylureas in the totally depancreatized animal (40, 41) or human being (21, 42, 43), nor in the fully alloxanized animal (21, 28, 40, 44).

(b) The clinical application of these compounds to the juvenile or labile type of diabetes has been notoriously unsuccessful (10, 12, 45).

(c) The usefulness of these compounds varies with the amount of insulin available in the pancreas (45).

(d) Older, stable diabetic patients respond well to the action of these compounds. These subjects have been shown to have a relatively good reserve of pancreatic insulin (46).

(e) The action of the sulfonylureas has been potentiated by injection directly into the pancreatic artery (47, 48). This has also been denied (49).

(f) The hepatectomized animal is still responsive to the action of arylsulfonylureas (23, 26, 39, 44) but when both liver and pancreas are removed this responsiveness ceases.

(g) The growth of the beta cells of the pancreas has been stimulated by the administration of arylsulfonylureas (50).

These actions of the arylsulfonylureas are not concerned with a *potentiation of* insulin activity (14, 51–53). One investigator had originally thought that the arylsulfonylureas are active in the hypophysectomized-pancreatectomized dog, but was later unable to confirm this belief (52).

When all of the evidence is summarized, it would appear that the activity of the arylsulfonylureas is concerned with both pancreatic and hepatic function. However, the precise points of attack have not yet been determined.

In any event, the oral hypoglycemic agents should be used with caution. If the pancreatotropic hypothesis be correct, an eventual exhaustion of islet-cell tissue may be expected, unless the recent findings of improved cellular appearance and function observed by Loubatières (54) are confirmed. Interference with enzyme systems in the liver which are concerned with the production and release of glucose, may, after long periods of time, result in both functional and anatomic damage to that organ.

INFLUENCE OF THE ENDOCRINE GLANDS UPON THE ACTION OF ARYLSULFONYLUREAS

The principal action of the arylsulfonylureas is not mediated through the pituitary, thyroid or adrenal glands (14, 15, 42, 53, 55, 56). However, completely adrenalectomized rats and adrenal demedullated rats are more sensitive to the action of tolbutamide than are intact animals (57–59). This is probably due to the fact that epinephrine "blunts" the hypoglycemic effects of tolbutamide in the normal animal. Moreover, in an acromegalic patient with diabetes mellitus, ACTH has been found to inhibit the hypoglycemic action of simultaneously administered tolbutamide (55).

Apparently excesses of growth hormone do not interfere with the hypoglycemic action of the arylsulfonylureas, as the diabetes of acromegaly has been successfully controlled by them (55). As a matter of fact, tolbutamide has been said to inhibit the diabetogenic action of somatotropin (60).

A temporary depression of I^{131} uptake by the thyroid has been described following administration of either carbutamide or tolbutamide (53, 61–63).

CLINICAL APPLICATION

Oral hypoglycemic agents have now been employed clinically in Europe and the United States for the treatment of upwards of 750,000 diabetic patients. No one of these compounds behaves physiologically like insulin. They are not useful in all types of diabetic patients, nor under all conditions in which insulin acts satisfactorily.

Types of diabetes mellitus in relation to treatment with oral hypoglycemic agents

The oral hypoglycemic agents thus far employed in clinical medicine should not be used in the following types of cases:

1. *Juvenile, "labile" or "brittle" diabetics.* By juvenile diabetics are meant those subjects with diabetes who are under 25 years of age. As a class, these patients have very little insulin reserve in the pancreas, which has been one explanation for their failure to respond well to the arylsulfonylureas or the diguanides. It should be emphasized that many of these patients may become stable diabetics following many years of good control. In fact, we have seen this happen before the twenty-fifth year of life or the tenth year of the disease.

The older diabetic in whom the disease is labile or brittle responds to the oral hypoglycemic agents much as does the juvenile patients, and possibly for the same reasons. From a biochemical angle we might regard these diabetics as subjects who can not manufacture or maintain a satisfactory reserve of insulin in the pancreas.

2. *Diabetes following pancreatectomy or complete destruction of the islets of Langerhans by pancreatic disease.* We have already discussed the ineffectiveness of the oral hypoglycemic agents in the total absence of the islet cells of the pancreas.

3. *Diabetics with acute infections and those with ketosis or acidosis.* In the presence of infection or of ketoacidosis, an insulin inhibitor appears in the body fluids and tissues (Stetten factor). Large doses of insulin are required to overcome it,

if overcome at all. It is totally unresponsive to any of the known oral hypoglycemic agents.

4. *Diabetics with renal complications.* Renal complications may not be a contraindication to the use of the oral hypoglycemic agents, provided there is no acute renal disease and renal function is good. Nevertheless, the limited solubility of the sulfonamides and the diguanidines may, in the presence of inflammation, favor crystalluria and consequent renal shutdown. Certainly prolonged use should be associated with careful, periodic urinalyses and functional tests of renal capacity.

5. *The pregnant diabetic.* There has not been sufficient experience with the oral hypoglycemic agents in pregnancy to warrant any conclusion regarding their use in this condition. The transient suppression of thyroidal uptake of iodine should be borne in mind in relation to its influence upon the thyroid of the fetus. Admittedly, this is a transient and relatively harmless alteration in thyroid function in the nonpregnant subject, reversible while administration of the drug is continued. Nevertheless, we have no information on changes which may occur in the thyroid of the fetus as a result of this temporary alteration in thyroid function.

6. *Diabetics who are overweight and adhering poorly to the diet.* Most older, overweight diabetics require little or no insulin. In those who take insulin, it is the rule rather than the exception, that a well controlled, adequate but not excessive diet will result in good control of the diabetic state. Such patients should not be encouraged to use an oral hypoglycemic agent. It is clear that they do not need it.

Many obese patients with mild diabetes have been given insulin during some acute illness, and its administration has not been discontinued. An obese patient with very mild diabetes may tolerate as much as 100 units of insulin without showing ill effects (64) and yet need only a regulated diet for satisfactory control of the diabetes. All too many of the good results reported in conjunction with the use of oral hypoglycemic agents have been in patients who are already needlessly using insulin. Duncan implied this when he commented that approximately 8 per cent and no more of all diabetics were suitable for the application of these agents (64). Despite this, a claim has been made recently that approximately 300,000 diabetics in the U. S. A. are daily employing a single one of these drugs. This represents not less than 20 per cent of all known diabetics in the country.

The ideal candidate for trial of an oral hypoglycemic agent is the relatively normal or underweight patient with mild diabetes, in whom glycosuria develops shortly after insulin has been discontinued but in whom ketosis develops only after a relatively long period of poor control.

Overall results in mild to moderately severe diabetes requiring insulin

It is difficult to discuss the overall results of treatment with the oral hypoglycemic agents in terms of percentages of failures or of partially controlled and fully controlled subjects, as the material studied by various workers has varied considerably in kind from observer to observer. Many data have been recorded without due regard for the types of cases included, the criteria for grading, and

TABLE 1

A Comparison of Effective Doses of, and Toxic Reactions to, Oral Hypoglycemic Agents

Drug	Approx. No. of Cases on Which Data Based	Average Effective Daily Dose (mg.)		Serum Half-life	Toxic Reactions
		Initial	Maintenance		
				hours	(%)
Carbutamide	8000	1500	1000	40	5.5
Tolbutamide	8000	2000	1000	4.5	2.8
Chlorpropamide	1000	500	300	40.0	8.0
Metahexamide	300	300	150	20.0	0.3
Phenethyldiguanide	300	300	150	5.0	25.0

the relation of results to the level of dosage used. However, if we include only the type of case just mentioned, the chances for successful control are approximately identical with each of the sulfonylureas. In about three-fifths to two-thirds of all diabetics requiring between 5 and 30 units of insulin daily and maintaining optimal or even slightly excess weight, the disease can be controlled with average amounts of the selected sulfonylurea, as noted in Table 1 and Figure 4. If the patient can tolerate the drug, the same statement applies to the use of the biguanide, DBI.

For the individual drugs, average initial and maintenance dosages will vary (Table 1 and Fig. 4). The range of effective daily dosage varies considerably from patient to patient. Whereas the requirements of some subjects will be either more or less than the dosages listed, the majority will fall between the following limits: for carbutamide, 0.5 to 1.5 Gm.; tolbutamide 0.5 to 2.0 Gm.; chlorpropamide, 0.1 to 0.5 Gm.; metahexamide, 0.1 to 0.5 Gm.; and DBI, 0.05 to 0.3 Gm. To achieve good control, tolbutamide and DBI, because of their serum half-lives of 4.5 and 5.0 hours respectively, should be given in fractional doses three times daily; the other drugs need not be administered more often than once daily. Indeed it is quite likely that chlorpropamide may be taken every other day (65).

Although a great deal has been written about the relationship of response to the duration of diabetes and to the age of the patient at the onset of the disease (66–80), there is no good "rule of thumb" which will indicate beforehand whether or not a case will respond well (67, 69, 76, 79). However, it is clear that highly "labile" subjects are not suitable for treatment with the oral hypoglycemic agents.

Single-dose tests of lowering the blood sugar level are misleading when used as a guide to therapy with oral hypoglycemic agents. If one must employ something of this sort, perhaps that devised by Duncan (72) is the best, as it requires a minimum of time and discomfort on the part of the patient, is relatively inexpensive, and is not too time-consuming for laboratory personnel. Even here, it seems that random trial is about as easy and certainly far more informative. If, on discontinuing insulin, ketosis develops rapidly (that is, within two or three days), it

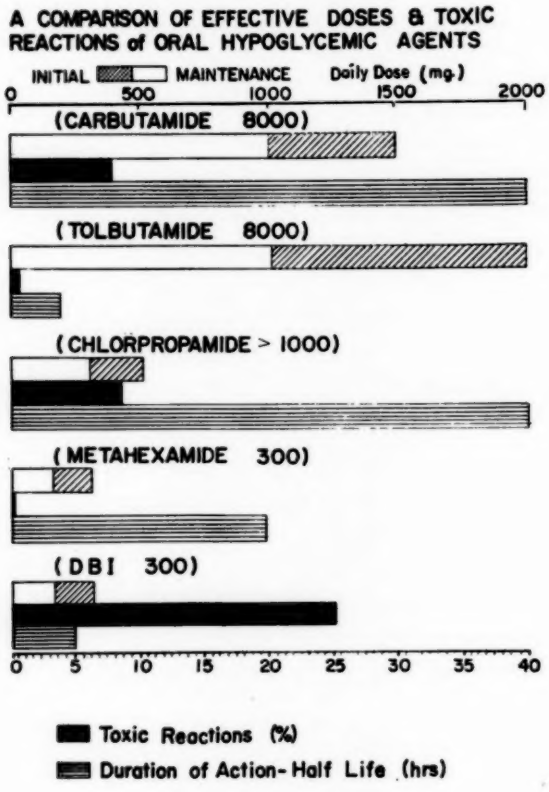


FIGURE 4

is not likely that any of the oral hypoglycemic agents will be useful, although specific claims have been made for the added value of DBI (81) and of chlorpropamide (16) in such a situation (6, 16).

Although increasing the dose of the oral hypoglycemic agent will sometimes increase the efficiency, this is true within rather narrow limits, and is not capable of expression in mathematical terms. Moreover, there seems to be no way of predicting to what extent the oral hypoglycemic agent will replace a previously required dose of insulin. In one subject, even the largest doses of the oral drug will serve to eliminate the need for only 5 or 10 units of insulin, whereas in another instance, average or even small oral doses will permit the patient to give up the injection of as much as 70 units of insulin daily (82). In view of these facts, it seems simplest to *prove* the need for something more than dietary control in any given subject and then try the influence of the oral hypoglycemic agent of choice.

Because of the demonstrated action of the oral sulfonylureas upon the secretion and/or release of insulin from the pancreas, it was suggested earlier that a "wearing off" of this action might occur. This has been fully confirmed for every compound thus far used clinically in this country, with the possible exception of metahexamide. The exception may exist only because metahexamide has not been employed a sufficiently long time to observe its ultimate effects. In the

case of the other oral hypoglycemic agents it usually takes not less than three months to observe the failure in response, but in some cases it may be delayed or may not even occur. It is interesting that administration of another compound of the same group will often elicit a full response (77, 83).

In the present state of our knowledge of the oral hypoglycemic agents, it would seem that the selection of one of these compounds depends more upon the nature and incidence of the side-effects from optimally effective therapeutic doses than upon any qualitative difference in the mechanism of action. In Table 2 and Figure 3 is shown a comparison of the untoward effects of the 5 oral hypoglycemic agents which have been extensively used in this country. For carbutamide, tolbutamide and chlorpropamide, the data are based upon the reports of several conferences devoted to these specific agents (84–86), and for metahexamide and DBI upon personal experience, personal exchange of information, and the papers of Williams *et al.* (5), Pomeranze (81, 87) and Krall *et al.* (88, 89).

Carbutamide was discarded for further use in this country, not so much because of the total overall incidence of side-effects, but because more than 2 per cent of the reactions were severe. Among nearly 8,000 fully analyzed cases, there were 8 deaths—2 from sulfonamide sensitivity, 2 from hepatic involvement, and 4 from extensive focal interstitial myocarditis. Liver damage was apparently present in all of the fatal cases and in a number of other patients with associated dermatologic or hematopoietic conditions. Gastro-intestinal manifestations were also present in several instances. In Table 2 and Figure 4 the initial or major presenting manifestation is indicated rather than the secondary, albeit serious, complicating features. There were 6 patients with severe exfoliative dermatitis, and 67 with hematopoietic disturbances, one of severe degree. Among the "other" side-effects were such subjective complaints as weakness, paresthesias, tinnitus, headaches, dizziness, and intolerance to alcohol.

TABLE 2

Toxic Reactions to Oral Hypoglycemic Compounds

Drug	Nature of Side-Effects (% Total No. Cases)							
	Total	Skin	Blood	Fever	Liver	Gastro-intest.	Death	Other
Carbutamide	5.5	1.5	1.1	1.2	−+*	+*	0.01	1.6
Tolbutamide	2.8	1.0	0.2			1.1	1 case	0.5
Chlorpropamide	8.0	5.0	0.1	0.1	0.3	2.1	1 case	0.3
Metahexamide	0.3	0.3						
Phenethyldiguanide	25.0					25.0†	?	?

* From available data it is difficult to calculate the actual percentage of gastro-intestinal and hepatic manifestations caused by carbutamide. The former, although troublesome, were usually not severe; the latter were rare but always serious.

† Investigators reporting work with phenethyldiguanide referred all untoward symptoms to the gastro-intestinal tract, yet many of the descriptions are indicative of vasomotor disturbances, and sometimes of peripheral vascular shock. These are not hypoglycemic reactions, as the blood sugar level may be high when they occur

The overall incidence of side-effects with tolbutamide was 2.8 per cent in a series of approximately the same size as that from which the present data on carbutamide are derived. One fatality has been reported (90) but there is considerable doubt as to the causal relationship of the drug to the death of this 84-year-old man. None of the remaining reactions was recorded as severe. There was no instance of agranulocytosis, exfoliative dermatitis or fever. Hepatic function was not disturbed. Most of the side-effects were mild, and disappeared either after a short omission of therapy or while therapy was continued, usually at a lower level of dosage.

The overall percentage of reactions to chlorpropamide may be too high (Table 2, Fig. 4), as this value was derived from the incidence of side-effects in the more than 1000 patients discussed in the recent Conference on Chlorpropamide and Diabetes Mellitus (86). Moreover, most of the cases demonstrating a reaction were probably detailed in the reports of the various authors, whereas some uneventfully treated cases may not have been included. The only death attributed to chlorpropamide was associated with toxic hepatitis in a patient employing a high dosage of the drug—2.0 Gm. daily. However, jaundice was reported in 3 other patients, and liver function was demonstrably altered in additional patients. Despite the high overall incidence of side-effects ascribed to chlorpropamide, most of the reactions were mild dermatologic phenomena with rarely any recognizable disturbance of the bone marrow and never agranulocytosis. Few if any of the reactions necessitated complete discontinuance of the drug. When only the untoward effects associated with commonly effective dosages are included, the incidence will undoubtedly be lowered.

The only side-effects observed in more than 300 patients treated with metahexamide were skin rashes in 2 subjects. The rashes disappeared when the dosage was lowered. Undoubtedly there will be further instances of toxicity as the drug undergoes more prolonged usage. There is no reason not to expect reactions similar to those described for other sulfonylureas, but the present indication is that these will not be severe.

In more than 300 patients, DBI has caused a surprisingly large number of untoward effects. Most of these have been attributed to action on the gastro-intestinal tract; they include anorexia, nausea, vomiting, diarrhea, dizziness, headache and profuse sweating, and sometimes a shock-like state. The latter may be easily mistaken for hypoglycemic shock; however, it occurs when the blood sugar level is little altered, so obviously it must represent a true, unwonted effect. Gastro-intestinal intolerance for this drug may prevent its widespread use, though hepatic function tests have failed to reveal any abnormalities.

SUMMARY AND CONCLUSIONS

Five oral hypoglycemic agents are being tried clinically in this country. Carbutamide has already been discarded as too toxic for human use. Tolbutamide has been extensively employed in as many as 300,000 diabetics according to its manufacturer. Chlorpropamide has recently been released for general use. Metahexamide has been administered to several hundred patients in Europe

and to about 300 in this country; prospects for its widespread application seem promising. Of the guanidine derivatives, synthalin was tried in the late twenties and considered to be too toxic for human use because of the incidence of hepatitis. Its congener, DBI, is also poorly tolerated by the gastro-intestinal tract, although no serious involvement of the liver has as yet been recorded in a limited number of cases.

None of these oral hypoglycemic agents is a substitute for insulin. All of them act upon both the pancreas and the liver, but the nature of the activity is still obscure. They are useful in a small percentage of diabetics of the so-called "stable" type, who require both insulin and a well controlled diet to maintain optimal health. The long-term effects on the capacity of the pancreas to produce insulin and on the enzyme systems of the liver concerned with carbohydrate metabolism are not yet known.

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HOST-TUMOR ANTAGONISM. XIV. SARCOMA OF THE SOFT TISSUES TREATED BY BACTERIAL TOXINS: UNSUCCESSFUL SERIES*

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The late John F. Mahoney, in a critique entitled *Cancer Research—Does it Help You?*, made the following statement: "The true estimate of the ability of a given chemical substance to influence the course of a malignant growth may be arrived at only after a protracted and painstaking effort. But unless this course of laborious study is carried out, the future may show that an effective curative agent had been available for many years, but its capacities unrecognised due to lack of careful scrutiny. If this happens it represents the worst type of tragedy." (71a).

It may be that bacterial toxin therapy in appropriate cases is just such an effective agent. Although the results, until very recently, did not measure up to those achieved in the early years (using Buxton or Tracy products correctly administered), a potent preparation is available at the present time[1].

The late Dr. William B. Coley was the first to use mixed bacterial toxins in the treatment of tumors. He believed that their action was not directly on the tumor, but through a possible immunologic mechanism involving the production of antibodies which cause unfavorable conditions for the life and growth of the tumor cell.

Shwartzman and Michailovsky (97b) thought that the effect of bacterial toxins on tumors was similar to the phenomenon of local tissue reactivity to bacterial filtrates—the so-called Shwartzman phenomenon. Different authorities have attempted to explain the hemorrhage found in the treated tumors, but it appears to be simply secondary to the degeneration and disintegration of the tumor cells which often form the boundaries of vascular channels.

It is possible that the mechanism of action of the mixed toxins may be entirely different from that already discussed. It has been shown by Landy and Pillemer (65a) that the injection of bacterial lipopolysaccharides derived from a variety of Gram-negative bacterial species evokes in mice a rapid rise in resistance to infection with Gram-negative pathogenic bacteria. This is accompanied by an elevation in the titer of properdin to levels two or three times normal.

In 1954 Pillemer *et al.* (87a) isolated a new euglobulin in serum, which they called properdin. In the presence of complement and magnesium, this protein

* Parts I–XII of this study were published in the July, August, November (1956), April, May, June, August, October, November (1957), May and July (1958), and May 1959 issues of the Journal.

Part XIII (the companion paper to Part XIV) dealt with the successful series of sarcoma cases treated with bacterial toxins. It was published in the August 1959 issue of the Journal.

† Drs. Pelner and Fowler are members of the Scientific Advisory Council.

[1] This preparation, together with detailed directions for administration, may be obtained from The New York Cancer Research Institute office.

destroys bacteria, neutralizes viruses, exerts a lytic effect on erythrocytes, and is readily destroyed by total body radiation. Herbut and Kraemer (59a) theorized that since total body irradiation may destroy an animal's ability to resist heterologous tumor transplantation, this resistance may work through the properdin system. They neutralized the animal's store of properdin by giving it zymosan, an extract of yeast-cell walls which combines quantitatively with properdin. They used normally resistant Wistar rats and attempted to implant human colon carcinoma HR 132. Of the 160 animals in each category, the number of tumor "takes" was as follows: 19 in untreated animals, 136 in irradiated animals, 58 in animals given a single injection of zymosan, and 90 in animals given multiple injections of zymosan. These findings indicated that the properdin system is involved in resistance to heterologous transplantation of tumors.

Southam and Pillemer (98) found that the properdin level was definitely depressed in 17 cancer patients whom they tested. Thus properdin is probably also involved in resistance to spontaneous cancer. If a constituent of the Coley toxins, *e.g.*, one of the bacterial polysaccharides, can elevate the titer of serum properdin, then the use of the toxins can be said to be a scientific, rather than an empirical treatment. This would directly confirm Coley's original idea of the mechanism of action of the toxins, which was at that time incapable of proof.

Recently two very interesting articles have appeared on the treatment of experimental sarcoma with mixed toxins.

Donnelly, Havas and Groesbeck (48) found that the mixed bacterial toxins of *Streptococcus pyogenes* and *Serratia marcescens* produced necrosis in Sarcoma 37 when given by the intraperitoneal route to mice which had the growing tumor implanted subcutaneously. The mixed toxins acting on Sarcoma 37 caused profound changes in the tumor cells, *viz*, edema of the cells, pyknosis of the nuclei, shrinkage of the cells, and disintegration. Hemorrhage into the tumor and eventual sloughing of the tumor occurred, with subsequent healing and scar formation. The mixed toxins also caused a general reaction which was more marked in the tumor-bearing mice.

Havas, Groesbeck and Donnelly (59) reported that the mixed bacterial toxins (*Streptococcus pyogenes* and *Serratia marcescens*) had a greater oncolytic effect than either agent used singly. They believed that the exotoxin of one organism and the endotoxin of the other were synergists and potentiated each other. They concluded that the apparent synergy inherent in the mixed toxins and missing in the purified bacterial polysaccharides justified continued investigation of this form of biotherapy.

FACTORS INFLUENCING PROGNOSIS

The following factors influencing prognosis in cases treated by toxin therapy (Coley toxins) seem of importance (see Appendix, Series C).

The stage of the disease when toxin therapy is begun

A high proportion of successful results (67 per cent) was obtained in primary inoperable cases with metastases. Of the recurrent inoperable cases, 51 per cent were successfully treated, but only 25 per cent when metastases were present.

Metastasis appears to affect prognosis much more than does cachexia or "poor general condition." Every patient in the operable group receiving adequate toxin therapy remained free from recurrence five years or more.

Other treatment given prior to toxins

Whether or not they were operable or inoperable when the toxins were begun, cases in which three or more surgical operations had been performed, or in which heavy, prolonged radiation had been administered prior to the toxins, did not respond nearly as well to subsequent toxin therapy as did cases which had not been treated previously.

Age and sex of the patient

The highest percentage of successes occurred in females aged 10 to 20, and 50 to 60 years; the lowest percentage was in males between 40 and 50 years of age. Taking all males regardless of age, only 40 per cent were successfully treated, as compared to 59 per cent of the females. It would appear that the majority of the males between 20 and 50 years old received less prolonged toxin therapy because of their desire to return to work, whereas this factor did not play a part for most of the females. However, another point should be considered: most physicians gave the same dosage to females as they did to males, although males weigh more than females. Thus the females received a slightly larger dose per pound of body weight than did the males.

The type of toxin used (Fig. 1)

It is now apparent that the Buxton's Type VI and Tracy's X and XI were the most potent and least variable preparations available during the period covered by this study, 1892–1953 (77–80). It is not surprising, therefore, to find that the highest percentage of favorable results was obtained in patients treated with one of these 3 preparations[2].

Duration of toxin therapy

This factor appears to be of great significance in treating inoperable cases, or when using a less potent preparation. Occasionally a permanent favorable result was obtained with the weaker preparations if they were given persistently in a dosage adequate to produce the desired reaction, and begun before metastases were present. Among the operable cases the majority of successful results were obtained in patients treated for six weeks to nine months. In the inoperable cases the optimum duration appeared to be from six to twelve months. It is noteworthy that if recurrence or metastases had developed following a brief period of toxin therapy, a permanent result could be finally obtained if toxins were promptly resumed and given persistently. For examples, see Cases 1, 5, 39, 41, 56, 57, 66 and 67 among the inoperable successes, and Cases 12, 16, 21, 22

[2] A considerable number of letters and reports are on file in the office of the New York Cancer Research Institute relating to the comparative weakness of the commercial preparations and the greater potency of the Buxton and Tracy products.

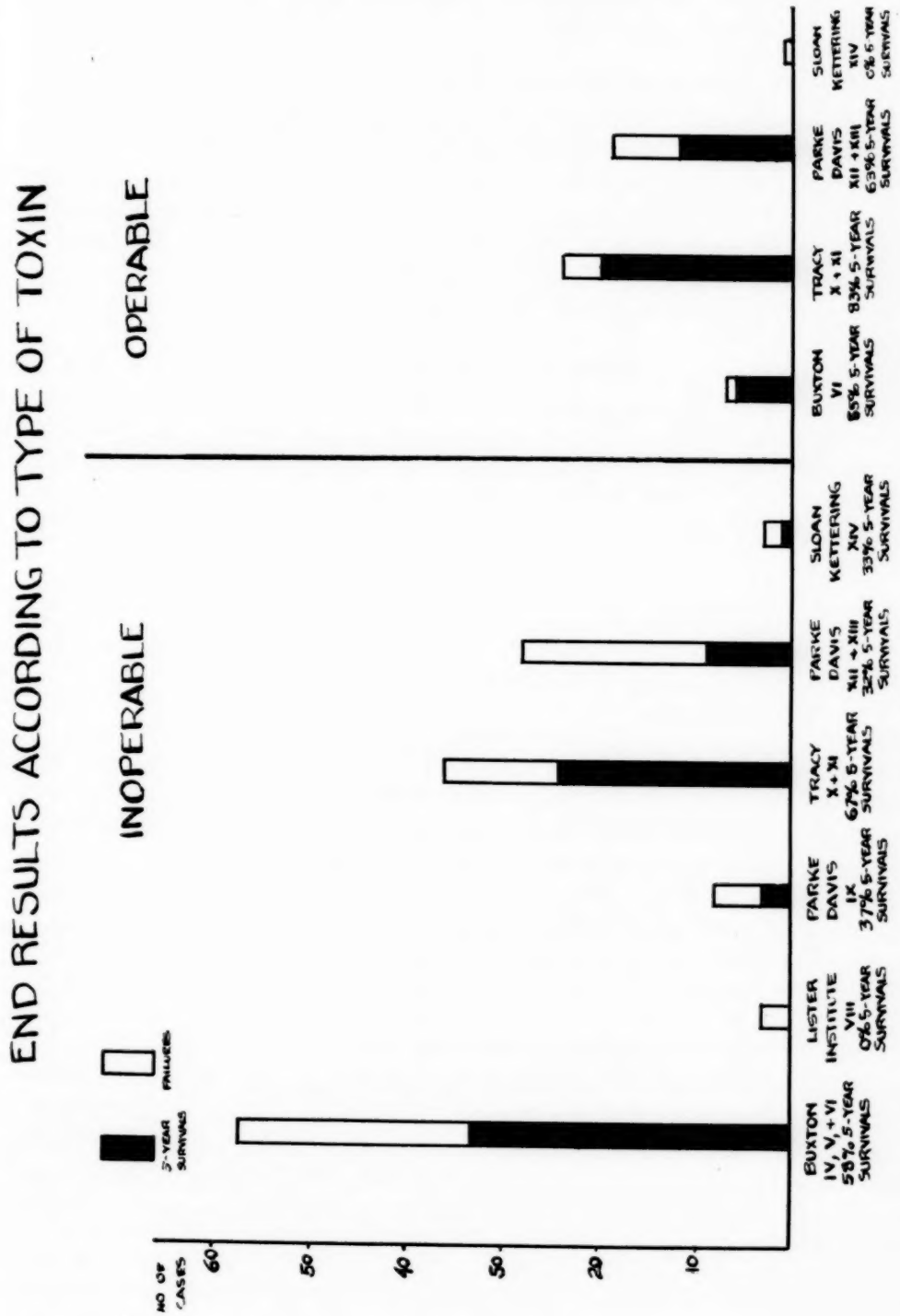
END RESULTS ACCORDING TO TYPE OF TOXIN
INOPERABLE
OPERABLE
5-YEAR SURVIVALS
FAILURES
NO OF CASES
60
50
40
30
20
10
BUXTON IV, V, + VI 58% 5-YEAR SURVIVALS
LISTER INSTITUTE VIII 0% 5-YEAR SURVIVALS
PARKE DAVIS IX 37% 5-YEAR SURVIVALS
TRACY X + XI 67% 5-YEAR SURVIVALS
PARKE DAVIS XII + XIII 32% 5-YEAR SURVIVALS
SLOAN KETTERING XIV 33% 5-YEAR SURVIVALS
BUXTON VI 85% 5-YEAR SURVIVALS
TRACY X + XI 83% 5-YEAR SURVIVALS
PARKE DAVIS XII + XIII 63% 5-YEAR SURVIVALS
SLOAN KETTERING XIV 0% 5 YEAR SURVIVALS

FIGURE 1

and 29 among the operable successes (Pelner, L., and Fowler, G. A.: *J. Am. Geriatrics Soc.* **7:** 624 (Aug.) 1959).

Type of reaction elicited and site of injection

Reactions were more marked, less prolonged, and better tolerated by the patients when injections were given into or near the tumors, or intravenously in doses sufficient to produce marked reactions with chills and temperatures of 101° to 104° F. or more. The highest percentage of successful results in the inoperable cases was in patients who had this type of reaction. In the operable series the results varied only slightly as regards injection into or near the cicatrix or tumor, intramuscularly remote from the tumor, or a combination of these two routes.

Several surgeons who described the technic they used advised injections in the vicinity of the growth and gradually into the tumor itself: these include Coley, Matagne, Odier and Wyeth (who also used living cultures of streptococcus injected into the wound following surgical removal of sarcomas). If tumors were inaccessible, *i.e.*, in the abdominal cavity or pelvis, they advised injections into the gluteal region or into the abdominal wall in the immediate vicinity of the neoplasm.

Frequency of the injections

In the majority of successful cases, injections were given every twenty-four to forty-eight hours during the first part of the treatment.

EFFECTS OF TOXIN THERAPY

Effects of toxin therapy on normal tissues or organs

A careful analysis of all the cases of sarcoma of the soft tissues and of about 800 cases of other types of neoplasms in which the toxins were used indicates that Coley toxins had no deleterious effects on normal tissues or on the kidneys, heart, liver or other organs. One patient with chronic Bright's disease responded satisfactorily to the toxins without any ill effects on the diseased kidneys (Case 30, inoperable successes.).

Stimulus to wound healing and regeneration of bone

Many surgeons noted remarkably rapid wound healing in patients who were receiving toxin therapy. Others noted that large areas of bone which had been destroyed by the neoplasm became completely regenerated, mostly in cases of bone sarcoma. (See Case 63 inoperable successes, for an example in the soft-tissue group. This patient had had parts of two ribs resected at the time of the exploratory operation.)

Relief of pain

A great many surgeons noted that there was marked relief of pain almost immediately after the injections were begun. In a few cases pain returned as

soon as the toxins were stopped temporarily, and again disappeared when they were resumed. Patients requiring large doses of narcotics were able to stop taking them. Relief of pain occurred even in patients in whom the disease was too far advanced to respond markedly to toxins, and who were not ultimately cured. This suggests that toxin therapy may be of value as a palliative in such cases.

Cessation of hemorrhages

A few physicians noted that in patients in whom hemorrhages had occurred prior to toxin therapy the hemorrhages ceased when toxins were administered. However in 2 far-advanced cases, necrosis of the tumor following toxin therapy caused fatal hemorrhage from a vessel in the growth.

Stimulation of hematopoietic tissues

There are a few case histories which suggest that the toxins may stimulate the hematopoietic tissues. (For an example, Case 63 among the inoperable successes.) This effect is sometimes masked by the anemia resulting from absorption of large quantities of necrotic tumor tissues.

Effects on concurrent pregnancy, and the fetus

Only 3 pregnant women are known to have received Coley toxins during pregnancy. The first such patient was Case 12 among the inoperable successes. She was given intramuscular injections of toxins during the second trimester of pregnancy; there was complete regression of the sarcoma. A normal child was born at full term. A second patient with far-advanced malignant melanoma also received the toxins intramuscularly during the latter half of pregnancy. There was marked palliation as regards relief of pain and improvement in sleep; there was also some evidence of temporary arrest of the extensive growths. Her child was born at about full term (labor was induced), and was entirely normal. The third patient, who had a reticulum-cell sarcoma of the humerus, was given a fairly large initial dose of toxins intravenously in the sixth month of pregnancy. This caused a marked reaction; the temperature reached 105.4° F. within two hours, preceded by a severe chill which began immediately after the injection. An abortion occurred a few hours later. The toxins were resumed nine days after abortion and given concurrently with x-ray therapy (2,000 r). Complete regression of the tumor followed. The patient was seen twelve years later, alive and free from disease.

Dangers of toxin therapy

The available evidence suggests that Coley toxins are without harmful or dangerous effects on patients or animals suffering from various types of neoplasms, provided these toxins are administered properly as to dosage and site and with the usual aseptic precautions. They should not be given to: 1) patients with severe hepatic insufficiency due to metastatic disease or other pathologic lesions, 2) patients who have had severe heart conditions, or 3) to patients

who are almost moribund. Such patients do not respond, and it is not even possible to elicit the desired febrile reactions.

CURRENT RESEARCH ON TOXIN THERAPY

During the past five years the New York Cancer Research Institute has been investigating various factors which appear to stimulate the natural resistance of patients or animals to neoplastic disease. In this connection, the apparently beneficial effects of bacterial products (Coley toxins) are being evaluated.

The first objective was to obtain a bacterial product which would be more potent as regards tumor destructive properties, without being more toxic to the patient or animal. Over 100 variations in formulae were tested, using virulent, freshly isolated strains of streptococcus, combined with *Serratia marcescens*. The most effective of these, based on extensive experiments on animal tumors, is being administered to patients with inoperable cancer and to certain patients with operable cancer before and after operation, as a prophylactic to prevent recurrence or metastases[3].

FAILURES OF TOXIN THERAPY IN THE TREATMENT OF SARCOMA OF THE SOFT TISSUES

An analysis of "failures" in the toxin therapy of inoperable sarcoma of the soft tissues (exclusive of lymphosarcoma) has been made. Some of these patients whose treatment with mixed toxins was considered a failure lived for twenty-two, nineteen, fifteen, ten, and five years after onset of the disease and almost as many years after toxin therapy was started. It may perhaps be said that we set our sights too high. Some of these cases should be considered as at least partial successes, even if the patients died with cancer. A recent monumental work by Pack and Ariel (86a) speaks of a woefully small five-year cure rate. Actually it would have been better to have considered these patients as five-year survivals without cancer. An extremely small number were alive ten and fifteen years later without cancer. It can be definitely stated that a patient with sarcoma rarely dies from the initial lesion or from a local recurrence, but from metastases.

Many factors besides those under direct control of the physician may change the picture radically. For example, there is general agreement that accidental injury or incisional biopsy can initiate a phase of intensive growth in a previously dormant tumor. With rapid growth, an invasion of the luxuriant blood supply by tumor emboli is a simple matter.

Fourteen of the cases were terminal when the treatment was begun, and 11

[3] This potent preparation was developed by Dr. Barbara Johnston, Project Director of the New York Cancer Research Institute, Inc. It is being made available to physicians who have used toxin therapy in the past, or who are now beginning long-term research on this form of therapy in the treatment of neoplastic diseases.

patients were already cachectic or in poor general condition. Although these may be counted as failures, they should perhaps be considered as instances of "compassionate" therapy. Some of the patients listed in the category of "failures" were treated with a potent product, but many received the weak toxins available at the time of treatment. In some, the potent toxins were used for an extremely short period. In a few, a potent product was used for a short time, and then resumed after a recurrence had taken place. How the patients would have fared had the toxins been used continuously without interruption for six or seven months longer is a matter for speculation. Early discontinuance of therapy was a great mistake inasmuch as complete regressions were recorded after persistent use of the potent toxins even for tumors that had recurred after cessation of initial therapy. Incomplete regression was noted in many cases. In 9 patients there was extensive necrosis and sloughing of the tumors, which contributed, and in some cases caused the death of the patient. A few patients died of toxemia due to absorption of large amounts of necrotic tumor tissue. These cases suggest the need for establishing drainage surgically or for incomplete removal of some of the tumor in order to avoid these problems.

Several of the patients died from hemorrhage, probably because a collapse of the sarcomatous tissue resulted in bleeding from a large vessel that was involved in the growth.

Some patients received large amounts of radiation before or during toxin therapy. It is probable that large amounts of radiation reduce the properdin level of the blood serum, and in this way defeat the effects of the toxins. Although we know that heavy radiation therapy is associated with failure of toxin therapy, a causal relationship is not as yet directly proved.

In some instances the toxin treatment was associated with marked relief of pain, although the final result was a failure. A few patients in whom treatment was a failure died from such causes as typhoid fever, radiation necrosis, and uremia due to blockage of the ureters by tumor tissue.

In a certain number of patients, it seemed that toxins prolonged life beyond the expected survival period. One patient lived twenty-two years after toxin therapy was started, and several others lived for six years afterwards.

Series C: Inoperable sarcoma of soft tissues (67 cases)

In Table 1 are listed the failures of toxin therapy in patients with inoperable sarcoma of the soft tissues (Series C). An analysis of the data for Series C is given in the Appendix.

Series D: Operable sarcoma of soft tissues (14 cases)

The following 14 cases of operable sarcoma of the soft tissues were unsuccessfully treated by Coley's toxins before or after operation. The first 7 tumors were primary and the last 7 were recurrent, at the time toxin therapy was begun. Nine of these patients had also received a considerable amount of radiation. (See page 717 for case abstracts.)

TABLE 1

Series C: Failures in Cases of Inoperable Sarcoma of Soft Tissues Treated by Bacterial Toxins

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
1. Lloyd & Coley (9, 12, 13, 41)	F 20	Spindle-cell sarcoma (tendon sheath?)	Palm of hand, 5 times recurrent; axillary metastases	Five operations prior to toxins; incomplete curettage during toxin therapy	Type IV, spring 1893; stopped during summer; resumed Oct. 1893, i.m. or near growth in hand; treated as ambulatory case by Lloyd; hospitalized by Coley	When toxins given steadily in adequate dosage, tumor decreased; after incomplete curettage patient gained 20 pounds; well 15 mos.	Further recurrence; amputation; died of brain metastases, 7 yrs. after onset (2½ yrs. after toxins begun)
2. Coley (16b)	M 48	Myxosarcoma	Thigh muscles, far advanced, recurrent; multiple tumors	Surgical removal	Type IV for 4 wks.; site not stated	Temporary decrease; later rapid growth	Death 4 mos. after toxins begun
3. Coley (2, 41, 73)	F 48	Sarcoma; type not stated	Face, orbit; exophthalmos; extensive involvement cervical glands	None prior to toxins	Buxton V & VI, 28 doses in 58 days; site?	Some regression	Died 2 yrs. after onset
4. Coley (16a, 73)	F 7½	Round and spindle-cell sarcoma	Ovary; twice recurrent, bilateral; trauma	Surgical removal of primary tumor and first recurrence	Buxton V, 10 doses in 3 wks.; site?	Considerable decrease in size	Contracted typhoid fever; died 6 wks. later
5. Coley (2, 41, 73)	M 43	Round-cell sarcoma	Recurrent, thigh; trauma; onset 4 mos. later	Surgical excision (incomplete)	Buxton V, 5 doses in 5 days begun 10 days after operation; site?; little reaction	Wound healed	Death 7 mos. after operation; "septic poisoning and sarcoma"
6. Andrews & Smith (1)	M adult	Sarcoma	Iliac fossa; extended ⅔ way to umbilicus; very extensive	Aspiration biopsy; later abscess opened freely irrigated with hydrogen peroxide	Buxton VI i.m. (ineffective); then into tumor every 48 hrs.; duration?	Tumor softened and broke down; immense abscess formed; much of tumor became necrotic	Life prolonged but died of exhaustion 8 mos. after onset
7. Rumbold (12, 16, 29)	F adult	Round-cell sarcoma	Breast; 7 times recurrent	Six operations prior to toxins	Buxton VI for 4 wks.; local injections?	Patient weak; persistent nausea; complete regression	Internal metastases developed; death (autopsy)

8. Coley (29, 108)	M 37	Spindle-cell sarcoma (myxosarcoma)	Chest wall; many times recurrent; infiltrating	Many operations; whole ant. chest scarred	Buxton VI for 3½ yrs.; with intervals of rest; site?	Complete regression	Well 8 yrs; recurrence; toxins resumed; biopsy; 12 x-ray treatments; necrosis whole upper sternum; death 4 mos. later
9. McArthur (13, 29)	F 5½	Round-cell sarcoma	Antrum of Highmore, nares, nasopharynx; exophthalmos; cervical gland metastases; bedridden; terminal	Stimulants, tonics; rectal feeding; after 2 wks. of toxins, cervical glands removed; 3 wks. later; primary tumor removed	Buxton VI every 48 hrs. for about 5 wks.; resumed after recurrence developed	Tumors became operable; severe exophthalmos diminished; patient gained 32 pounds; recurrence after toxins stopped; temporary improvement when resumed	Disease not controlled; death 2 mos. after toxins stopped
10. Coley (41, 73)	M 45	Spindle-cell sarcoma	Scapular region, 11 x 15 ins., ulcerated, recurrent; axillary involvement	Surgical removal of primary tumor; recurrence untreated	Buxton VI remote from tumor for 6 wks.	Slight regression; no marked effect (compare with Case 11 in Series A, inoperable successes)	Died 2 months later
11. Coley (3, 73)	F 62	Myxosarcoma	Abdominal wall, iliac region, 5 times recurrent; 9 x 9½ ins.	Five operations prior to toxins	Buxton V & VI; site? 39 doses in 3 mos.	Temporary arrest	Death 20 mos. after toxins begun, 12 yrs. after onset
12. Coley & Meixell (13, 16, 41, 73)	F 20	Sarcoma of tendon sheath	Palm of right hand, thrice recurrent; metastasis to axillary node; (trauma)	Two operations prior to toxins	Buxton V & VI for 3 mos. in arm (i.m.); resumed later for brief period	Complete disappearance; perfect function; 5 mos. later axillary metastasis excised; marked necrosis	Later, another recurrence; amputation; no further toxins; disease generalized; death 5 yrs. after onset
13. LaFetra & Coley (16, 16a, 16c)	F 48	Spindle-cell sarcoma	Thigh, groin, recurrent; edema entire extremity; (trauma)	Incomplete surgical removal; large mass in groin not touched; old scar removed after 2nd course of toxins: no evidence of tumor	Buxton VI begun 11 wks. after op.; given 3 mos.; resumed after further recurrence; site?	Pain ceased; complete regression; edema subsided, leg normal; recurrence 7 mos. later; another regression after toxins resumed	Later, another recurrence; no further treatment; death about 6 yrs. after onset
14. Harris (16)	F 31	Large round-cell sarcoma	Ovary, recurrent; size of coconut; obstruction; extreme distention; (terminal)	Panhysterectomy for primary tumor; recurrence untreated	Buxton VI s.c., increased to 40 minims; very little reaction; about 18 doses in 16 days	On 4th day, wound opened; almost normal bowel movements; in 3rd wk. tumor became gangrenous; fecal matter discharged through wound	Septic absorption from immense sloughing tumor; death about 4 wks. after toxins begun

TABLE 1—*Continued*

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
15. Willy (29, 41, 81)	F 42	Mixed-cell sarcoma	Uterus, broad ligament, recurrent; size of coconut; extensive adhesions; hemorrhages	Laparotomy; prognosis "few wks."; arsenic orally; pyoktanin injected into tumor	Buxton VI; later weaker Parke-Davis IX, given spasmodically for 6 yrs. by husband (physician); injections into tumor (cervical area) more effective	Prompt complete regression in 10 days; recurrence after toxins stopped; another regression when resumed; patient gained 22 pounds	Disease controlled 6 yrs.; patient returned to Europe; another attempt at removal; died on operating table
16. Coley (18b)	M 49	Spindle-cell sarcoma	Thigh; recurrent 9 mos. after operation	Extensive surgical removal year after onset; later, hip-joint amputation	Buxton VI for 3 mos.; site?	Marked regression at first; growth remained stationary, then increased again	Further recurrence; patient died 4 yrs. after onset
17. Nicholson (82a)	F 46	Round-cell sarcoma	Uterus, both broad ligaments; 32-pound weight loss	None; terminal case	Buxton VI every 48 hrs. for 15 days; some reaction; site?	No apparent benefit	Death 15 days after first injection of toxins
18. Meriwether (75a)	F 33	Small round-cell sarcoma	Apex of Scarpa's triangle, left; foul discharge; much pain	Mass lanced, then grew rapidly; patient had left-sided pleurisy	Buxton VI, briefly (patient objected); resumed; injected into primary tumor	Decreased 50%; after toxins stopped, primary tumor increased; cervical gland metastasis disappeared during further toxin therapy; primary tumor did not; another tumor appeared on left arm; regressed during continued toxin therapy	Disease not controlled; patient emaciated; death 5 mos. after toxins begun
19. Coley (16d, 73)	M 42	Round-cell sarcoma	Nares, antrum, recurrent; very rapid growth; frequent hemorrhages	Incomplete surgical removal; after toxins, external carotid tied, curettage	Buxton VI in or near growth (40 doses in 73 days); good reactions; 2 more courses after recurrence	Pronounced regression; hemorrhages ceased; sloughing of tumor in nasal cavity; recurrence when toxins stopped	Slow steady increase; death from hemorrhage at attempted removal (another hospital)

20. Coley (41, 73)	M 25	Round-cell sarcoma	Thigh, 5 x 8 ins.; terminal; (trauma, strain)	Exploratory op.; curetted twice; sinuses irrigated with K permanganate; later, surgical drainage	Buxton VI begun 8 days after 2nd currettage; given 9 wks.; site?; (fever prior to toxins)	No apparent benefit, but appetite remained remarkably good	Pulmonary symptoms; death 4 mos. after toxins begun
21. Coley (17a, 17c, 31, 73)	M 70	Round-cell sarcoma; very vascular	Neck, post. to scalenus anticus muscle, 5 times recurrent; size of orange; metastases, femoral, axillary, right cervical	Five operations; left ext. carotid tied after inital course of toxins; later x-ray therapy (6 wks.); complete regression of tumors in neck and axilla in 4 wks.	Buxton VI; only one reaction; given 3 wks.; resumed for 11 days (i.m.)	At first slight improvement; later no effect; patient discouraged, bored with hospital life	Further metastases in groins responded to further radiation; death from (?) cerebral thrombosis 15 yrs. after onset, 2 yrs. after toxins
22. Porter (29, 58)	F 40	Round-cell sarcoma	Left ovary, recurrent in pelvis	?	Buxton VI for 2 mos.; site?; toxins resumed when recurrent tumors developed; type? site?	Complete disappearance; patient remained well 4 years.	Recurrence not controlled; date of death not stated
23. Coley (17a, 41)	M 25	Round-cell sarcoma	Parotid, twice recurrent	Two operations prior to toxins; later ext. carotid tied; x-ray therapy	Buxton VI for 3 wks. in small doses; site?	At first, slight regression and considerable relief of pain; later, no effect	Death 6 mos. after onset
24. Emerson (52a)	F 64 (obese)	Spindle-cell sarcoma	Tonsil; 28-pound weight loss; (5 bloody discharges from left breast)	Tumor on forehead destroyed by caustic 4 yrs. previously; electrolytic needles in tonsil tumor; later several x-ray treatments	Parke-Davis IX or Buxton VI in tumor or arm twice weekly for 2 mos.; after recurrence toxins resumed (in arms, poor absorption)	Patient gained 25 pounds; only 1 more bloody discharge from breast; general health improved	Metastases developed; patient failed rapidly after toxins stopped; death 17 mos. after onset
25. Coley (18b, 18c, 20, 24, 41, 73)	M 16	Round-cell sarcoma	Chest wall; necrosis 8th & 9th ribs; onset followed pleurisy with effusion	Necrotic ribs; gelatinous masses partially removed; x-ray therapy thrice weekly same day as toxins; 2nd curettage (recurrence); profuse hemorrhage	Buxton VI for 2 mos. in region of wound; moderate to good reactions; 3½ mos. later Parke-Davis IX, 13 doses in 40 days; no reaction; 3rd course, 97 doses in 6 mos.	Complete regression; patient in excellent health; gained 25 pounds; then local recurrence	Disease progressed locally; death 2½ yrs. after onset
26. Shield (29, 94a)	F 44	Myeloid sarcoma	Breast, recurrent in scar and axilla, and beneath clavicle	Mastectomy; recurrence untreated	Lister Institute VIII, large doses into vascular tumor mass; some severe reactions; toxins given about 17 days	Marked relief of pain; larger growth disappeared in 17 days; smaller became half necrotic; mass under clavicle smaller; 2 days after last dose, staph. pyemia	Death from pyemia in 48 hrs.; autopsy; all tumors had disappeared or were necrotic; (toxin used was sterile)

TABLE 1—*Continued*

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
27. Battle (1b)	Not stated	Spindle-cell sarcoma	Peritoneum (abdominal)	Not stated	Lister Institute VIII intramuscularly in arm; 1 inj. into abdom. tumor	Abdominal measurements decreased 1 inch	Patient died after intra-abdominal dose
28 Rigby (41)	F 14	Spindle-cell sarcoma	Aponeurosis of left knee, involving periosteum; recurrent; metastasis to ilium	Exploration; biopsy; amputation; x-ray (30 treatments) begun 5 wks. after toxins; 13 more during 2nd course of toxins	Lister Institute VIII, 5 doses in other leg, rest into tumor; 47 doses in 120 days; good febrile reactions; toxins resumed after 3½ mos.	Gradual regression; immediate cessation of pain (before x-ray begun); pain increased when toxins stopped and ceased when resumed	Disease not controlled; mass in right groin; death 12 mos. after toxins begun, 4 yrs. after onset
29. Semken (41)	Young male	Mixed-cell sarcoma	Fascia of pectineus muscle over upper femur involving periosteum; recurrent; extensive	Primary tumor removed surgically; recurrence untreated	Parke-Davis IX, later Buxton VI; 24 doses in 76 days, usually into tumor but a few into abdominal wall s.c.; reactions more marked with VI than with IX	Tumor began to break down; patient became septic	Disease not controlled; death 4½ mos. after toxins begun
30. George & Warthin (54a)	M 73	Large spindle-cell sarcoma; adenocarcinoma of pylorus; adenomatous polyp; myomata	Right forearm (sarcoma); axillary metastasis; pylorus (ca.); polyp on cardia; myomata stomach wall	Incisional biopsy, arm tumor; no other therapy; condition hopeless; also arteriosclerosis, chronic bronchitis & nephritis	Parke-Davis IX into tumor every 24 or 48 hrs. for 41 days	Large areas necrotic at sites of injection, but tumor grew very rapidly peripherally; involved whole arm; abscess; septic poisoning	Death 3½ mos. after toxins begun; autopsy showed extensive necrosis in sarcoma and in metastasis
31. Parlett (2, 41, 73)	M 26	Sarcoma	Chest wall, pectoral muscles to clavicle; metastasis 4th finger right hand; recurrent tumor on hand	Incomplete removal twice; amputation of finger; x-ray treatments during toxin therapy; no effect; severe x-ray burn	Parke-Davis IX into tumor and shoulder for 15 mos.; resumed 3 mos. later for about 4 mos. with more x-ray therapy; final course	No improvement at first; another recurrence responded to toxins injected into or near tumor masses; patient in good condition; disease controlled over 6 yrs.	Patient died (pulmonary metastases) 9 yrs. after onset, 6 yrs. after toxins begun
32. Underson (41)	F, young adult	Spindle-cell sarcoma	Post-orbital region, involving left naris and roof of mouth	Biopsy; x-ray treatments after toxins	Parke-Davis IX daily, usually in shoulder muscles or cheek, for about 3 mos.	Growth ceased for about 4 mos.	Disease not controlled; death about 6 mos. after toxins begun

33. Coley (41, 73)	M 56	Small spindle-cell sarcoma	Deltoid muscle; twice recurrent in distal clavicle; scapular region, ribs, cervical glands (trauma)	Biopsy; excision; inter-scapulo-thoracic amputation; x-ray therapy week after toxins (4 a week); dissection of recurrent tumor	Parke-Davis IX locally every 24–48 hrs. in large doses; little reaction; given during radiation for about 6 wks.	Little improvement	Death 6 mos. later
34. Bull (21a, 41)	M 34	Mixed-cell sarcoma, vascular, extensive	Inner upper thigh; recurrent; patient very weak; 20-pound weight loss; bedridden; much pain	Exploration; large hematoma evacuated; spurting hemorrhage 3 days later; tumor removed; rapid recurrence untreated	Tracy X alternately into tumor and remote from it; toxins stopped because Dr. Bull became ill; no other physician available to treat patient	Immediate improvement; tumor broke down and rapidly drained large amounts of dark fluid; in 3 wks. mass of tumor 5 ins. in diameter separated and was easily lifted out; base clean; almost complete regression	Toxemia developed; control lost; death 2 mos. after first dose
35. Green (55, 81)	M 67	Small spindle-cell sarcoma; primary tumor highly vascular	Soft tissues of scapular region; twice recurrent	Two operations prior to toxins; 3rd after toxins (much less hemorrhage; tumor anemic, degenerated)	Tracy XI into arm and tumors, 12 doses in 4 wks.; resumed after 3rd op., twice weekly for 2½ mos. into arm and back muscles	Tumor less vascular, distinctly smaller; another recurrence 1 mo. after last dose of toxins; tumor regressed slightly; inactive	Lived 9 yrs. after toxins begun; died with sarcoma of cervical spine at age 76
36. Green (54b, 81)	F 37	Small round-cell sarcoma	Parotid region, involving sternomastoid; recurrent	Primary tumors removed surgically; recurrence untreated	Tracy XI into arm or tumors for 2 wks.; slight reactions	After 2nd dose injected into tumor, growth softer but larger; unimproved	Death 2 yrs. after onset, 6 mos. after toxins begun
37. Large (66)	M 45	Round-cell sarcoma, very vascular	Post-nasal region; nares occluded; bilat. optic neuritis; exophthalmos	Small section removed for biopsy	Tracy XI for 1 mo.; family then stopped treatment; resumed briefly	Within a month patient able to breathe through both nares; improving; severe headaches developed when toxins stopped, but were relieved when resumed	Death from cerebral metastases
38. Green (54b, 81)	F 2	Fibrosarcoma	Palate and upper jaw; patient in poor condition	Incision; profuse bleeding; section removed for biopsy	Tracy XI; 2 doses into tumor	Severe reaction to second dose (104° F.); temp. normal next day but rose to 102.6° F. that afternoon; patient grew rapidly worse	Death 3 days after 2nd dose; temperature 107.6° F. (no autopsy)

TABLE 1—*Continued*

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
39. Mitchell (61, 86a)	M 45	Round and spindle-cell sarcoma	Thigh, recurrent; metastases to lungs, liver, kidneys and mesentery; terminal	Exploration; considerable hemorrhage; area tightly packed; postoperative infection did not prevent recurrence	Tracy XI, 21 doses in 42 days; reactions 100°–104.2° F., once 105.2° F.	Tumor swelled and discharged large amounts of necrotic tissue	Disease progressed; death 5 wks. after 1st dose
40. Coley (29, 73)	F 16	Fibrosarcoma	Ovary (trauma); large recurrent growth filled pelvis and lower abdomen; much weight loss; cachexia	Primary tumor (6½ pounds) removed surgically; 2nd op. merely exploratory	Tracy XI given 5 wks.; marked reactions; resumed 3 wks., later for 1 or 2 wks.; month later 3rd course, 9 doses in 21 days, i.m.; no reactions	Complete regression in 8 wks.; toxemia from rapid absorption; diffuse pain over entire body, especially joints; patient lost 36 pounds; anemia; some improvement with final course	Disease not controlled; death 6 mos. after toxins begun
41. Large (66)	M 19	Round-cell sarcoma	Postnasal region, naris, upper jaw, all sinuses on left, extending into cranium; severe pain; exophthalmos	Growth probed; severe bleeding; incisional biopsy; eye enucleated and upper jaw resected (incomplete removal of tumor)	Tracy XI started 2 wks. after op. and given for about 3½ mos.; site?	Toxins held growth in abeyance; no pain during toxin therapy; excruciating pain after toxins were stopped	Death 2 mos. after toxin stopped
42. Rule (2, 41, 73)	M 21	Angiosarcoma	Nasopharynx; lymph node metastases; twice recurrent	Two operations; 2nd recurrence untreated	Tracy XI, minute doses into chest, shoulder and pectoral muscles; no reactions; given about 6 mos.	Patient improved steadily; gained 20 pounds	Later, multiple metastases developed; death 4½ yrs. after toxins begun, 9½ yrs. after onset
43. Harmer (58, 81)	M 42	Fibrosarcoma	Thigh, 4 x 5 ins., recurrent; also osteitis deformans	Exploration; mass size of orange removed; immediate recurrence	Tracy XI, every 2 or 3 days for 7 wks.; site?	Growth softer but not smaller; patient suffered from absorption of necrotic tumor	Rapid growth when toxins stopped; death a few weeks later
44. Boyer (41, 81)	F, adult	Endothelioma	Nasopharynx; recurrent	Surgical removal; rapid recurrence x-ray therapy ineffective	Tracy XI, usually daily for 6 wks.; at first into tumor; later into muscles	Growth arrested; then spread to deep cervical nodes	Neck dissection attempted; patient died on operating table
45. Harmer (41, 58)	M 22	Spindle-cell sarcoma	Thigh; thrice recurrent; rapid growth	Three operations prior to toxins	Tracy XI for 5 wks.; small doses; moderate, then severe reactions; site?	Tumor "broke" after 5 wks. of toxin therapy	Death 7 wks. after toxins begun; sudden severe hemorrhage from large vessel involved in growth

46. Coley (73, 81, 108)	M 50	Spindle-cell sarcoma	Retroperitoneal, 21 x 24 cm.; 20-pound weight loss	Exploration; biopsy; x-ray therapy twice weekly for 4½ mos.; sodium cacodylate (all prior to toxins)	Tracy XI, 14 doses in 24 days; no marked reactions; possibly continued at home briefly; site?	Disease arrested temporarily	Death regarded as due to carcinoma of pancreas 4 yrs. after onset of retroperitoneal mass
47. Lilienthal (81)	F 6 mos.	Small round-cell sarcoma	Left nose; upper lip	Specimen removed for biopsy	Parke-Davis XII daily i.m.; later, alternately into tumor and buttock; stopped during severe measles; resumed; total 6 mos.	No benefit until given into tumor; then slight decrease; growth stationary during measles; afterwards growth very rapid	Death 11 mos. after onset
48. Coley (2, 24, 41)	F 5	Endothelioma	Face, involving left upper jaw	Incision; Antiphlogistine applied; incomplete removal; KI given	Parke-Davis XII into tumor; then P-D, XIIF (filtrates) alternately into pectorals for about 6 mos.	Tumor softer and more movable; regressed some; patient gained weight; rapid growth each time toxins stopped	Death 18 mos. after onset
49. Mertz (41, 81)	M 42	Sarcoma; type not stated	Right mid-thigh, involving groin, popliteal space; thrice recurrent	Three operations; 3rd recurrence untreated	Parke-Davis XII into tumor masses, usually daily; slight reactions; given 6 mos.	Tumor masses regressed about 50%; severe pain after toxins stopped	Death 10 mos. after toxins stopped, 5 yrs. after onset
50. Lee (41, 81)	M 59	Sarcoma; type not stated	Cervical region	Biopsy	Parke-Davis XII into tumor and shoulder for 4 mos.	Patient improved at first; mass much smaller; breathing better	Later, no benefit; death
51. Harmer (58)	M 14	Sarcoma; type not stated	Thigh, invading pelvis; size of melon; sloughing (trauma)	None, apparently	Parke-Davis XII for 7 wks. into growth	Some disintegration of tumor at sites of injection; no marked effect	Death 6 mos. after onset; pulmonary, hepatic metastases
52. Allen (41, 81)	F 42	Myxosarcoma	Abdomen, pelvis; extensive; organs covered with growths; patient almost bedridden	Exploration; some tumors removed for biopsy; 4 radium packs	Parke-Davis XIII i.m. every 4–5 days for 18 mos.; very little reaction	Patient improved greatly; almost complete regression of tumor; then a bad fall; condition rapidly declined	Death 16 mos. after toxins begun
53. Gray (81)	M, about 40	Sarcoma; type not stated	Posterior mediastinum, far advanced; dull pressure pain; patient could not swallow	None?	Parke-Davis XIII into deltoid muscles about 2 wks.	Pain relieved; patient could swallow in few days	Sudden death due to collapse of tracheal wall from necrosis of tumor

TABLE 1—*Continued*

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
54. Coley & Cooper (41, 73)	M 49	Spindle-cell sarcoma	Retroperitoneal, very extensive; metastases to liver, intestines, parietal peritoneum; 35-pound weight loss	Exploration; biopsy; radium packs during toxin therapy (33,021 mch.)	Parke-Davis XIII, 4 doses a week (apparently i.m.) for 4½ mos.; no marked reactions	Within 2 wks. tumor smaller and softer; rapid regression, patient's general health improved markedly; gained 25 pounds; sudden fatal hemorrhage from vessel involved in growth	Death 9 mos. after onset; autopsy showed all metastases above umbilicus had disappeared, also those on liver and parietal peritoneum; primary tumor necrotic
55. Coley (73, 81)	F 27	Mixed-cell sarcoma	Maxilla, recurrent; 13-pound weight loss (trauma)	Local treatment with salves and poultices; excision; 3 x-ray treatments, also radium packs	Parke-Davis XIII, i.m., in very small doses; no reactions; given 8 wks. with intervals rest	No apparent benefit	Death 3½ mos. after toxins begun
56. Coley (2, 41)	F 50	Round-cell sarcoma; recurrent	Antrum, ethmoid, upper jaw; left eye closed; whole left malar area, left lateral nasal septum; right eye, divergent strabismus; pain; perforation	Nasal polyps excised; tooth extracted; incision of tumor; pus drained; excision; recurrences treated with radium needles, diathermy, fulguration, causing perforation	Parke-Davis XIII, 20 doses i.m. and 3 i.v. in 34 days; good reactions more than half the time	Almost immediate improvement; protruding fungating tumor largely disappeared, leaving opening at site of perforation at junction hard & soft palate	Disease not controlled; death 16 mos. after toxins begun
57. Cheney (2, 41)	F 45	Spindle-cell sarcoma	Calf of right leg; metastases to left cervical region and lungs (many large ones)	Excision; deep x-ray therapy	Parke-Davis XIII in small doses; no severe reactions; site? duration?	Definite improvement; much less dyspnea; general condition excellent	Disease not controlled; death 4 mos. after toxins begun
58. Pratt (2, 41)	F, adult	Fibrosarcoma	Thigh, lower internal third; recurrent	Excision; 46 x-ray treatments; recurrent tumor increased rapidly during radiation; amputation after toxins	Parke-Davis XIII (usually injected remote from tumor but some into it) for about a month, with intervals of rest	Decrease in size; surrounding tissues became softer but tumor did not	Mediastinal and lung metastases; death year after toxins begun

[illegible]	M	Large round-	Fascia of foot; recur-	X-ray therapy; arch sup-	Parke-Davis XIII into	Pain and edema relieved;	Disease not controlled;

59. Flock (2, 41)	M, adult	Large round-cell sarcoma	Fascia of foot; recurrent; metastases, inguinal femoral region; some edema of leg	X-ray therapy; arch supports; operation; more x-ray therapy for recurrence; metastases; recurrent tumor excised; 5 more x-ray treatments; no effect	Parke-Davis XIII into abdominal wall; later, into tumor or near it; 14 doses in 19 days; a few more after 2nd course of x-ray therapy	Pain and edema relieved; general condition improved markedly; left inguinal metastases reduced in size; 2 new ones appeared in skin	Disease not controlled; death year after onset, 4 mos. after toxins begun
60. Rilling (41, 81)	M 35	Spindle-cell sarcoma	Left leg, ulcerated; abdominal and hepatic metastases; obstruction; terminal	Numerous growths removed for biopsy	Parke-Davis XIII, 6 doses in 6 days; only 1 dose caused a reaction	No apparent benefit	Rapid increase in liver metastases; death 1 mo. after toxins begun
61. Coley (73, 81)	M 37	Myxosarcoma	Thigh, very extensive; abdominal metastases	Radium (8,000 mch.) x-ray (4 treatments) during toxin therapy; 1 more x-ray treatment later	Parke-Davis XIII i.m. and i.v.; 30 doses in 60 days	Gained 15 pounds during treatment; no regression evident until later; markedly improved temporarily; then both primary and metastatic masses increased greatly	Death 11 mos. after toxins begun
62. Wentz (41, 81)	F 50	Sarcoma	Breast, extensive recurrence involving thorax below clavicle; severe pain	Two operations; plasters applied; mastectomy; improved with collodaurum, cachexia disappeared	Parke-Davis XIII i.m.; later, into tumor; daily at first, then every 2 or 3 days for about 7 mos.	Complete regression; patient well for a few months, then became ill again	Death from multiple metastases
63. Coley (41, 73)	F 30	Malignant leiomyoma or fibrosarcoma	Sheath of rectus involving large intestine and bladder; twice recurrent; nodules in scars; condition hopeless; husband a suicide due to her illness	Primary tumor removed, also half of each ovary (cysts) and appendix; suspension op.; recurrence 5 mos. later; x-ray therapy aggravated it; 2nd op. for recurrence; radium (48,000 mch.)	Parke-Davis XIII i.m. (doses too small to be effective); later given more aggressively by Coley, into tumor; severe reactions; about 40 doses in 3 mos.	No effect until given into tumor; then mass became much smaller and more mobile; patient lost ground rapidly after radium therapy; tumor increased	Death 16 mos. after onset, 3 mos. after toxins begun
64. Coley (41, 81)	M 7	Malignant juvenile nasopharyngeal polypoid angiomyxosarcoma	Orbit, twice recurrent, involving sphenoidal fissure and ethmoid; very extensive; great pain	Excision; radium; intensive prolonged x-ray therapy for both recurrences; transfusion	Following x-ray therapy, patient had scarlet fever (tumor increased during it); Parke-Davis XIII and special Type VI i.m.; for 3½ mos.; good reactions	Pain ceased entirely 2 wks. after toxins begun; marked, rapid improvement in 4 wks.: tumor entirely necrotic; then continuous fever of 103°–104°F. due to absorption of necrotic tumor tissue	Improvement ceased; pain returned; death 1 mo. after toxins stopped, about 2 yrs. after onset

TABLE 1—*Continued*

Doctor and References	Sex and Age (yrs.)	Type of Tumor	Site of Tumor	Other Treatment Before or After Toxin	Type of Toxin Used; Site & Duration of Treatment	Immediate Result of Toxin Therapy	Final Result of Toxin Therapy
65. M. Hospital (73)	M 31	Leiomyosarcoma or possibly reticulum-cell sarcoma	Left thigh, recurrent; pulmonary metastases (both lungs); great natural resistance	Attempted excision; x-ray therapy to thigh (6,500 r), to back (6,100 r); patient well almost 6 yrs., then metastases to lungs; further local recurrence; intensive radiation of thigh and lungs (total, 34,800 r)	Parke-Davis XIII concurrently with next to final course of x-ray therapy; 14 doses in 14 days i.v.; marked reactions	Temporary good response to combined therapy	Death 2½ yrs. after lung involvement, 8½ yrs. after onset
66. Wehrly (81)	F 60	Leiomyosarcoma	Uterus; pulmonary metastases; diaphragm and pancreas also involved; terminal; in shock	Untreated; patient was a Christian Scientist	S.K.I. XIV, 4 doses in 4 days; first dose i.m.; others i.v.; slight reactions	No effect	Death 3 days after last dose, 13 mos. after onset
67. Wehrly (81)	F 46	Leiomyosarcoma	Cervix and broad ligaments, recurrent; lymph node metastases, bilat. int. iliac, along aorta, lower left lung; severe pain; emesis	Biopsy; panhysterectomy; iliac lymph nodes removed; x-ray therapy (3095 r to recurrence and 427 r to lung); radium to apex vagina (1,100 r); no benefit	S.K.I. XIV, 15 doses in 17 days; all but first dose, i.v.	Complete relief of pain; patient ate well; all lymph node metastases regressed completely; hydronephrosis developed; uremia due to blockage of ureters from tumor tissue	Death 3 days after last dose; autopsy showed much less tumor present than at op. 7 mos. before

Series D

Years traced

1. (Green[4]) *T. J. G.*, male, aged 24. Round-cell sarcoma of left arm above elbow; onset in June 1907; excision February 8, 1908; amputation refused. February 10, 1908, toxins (Tracy XI) begun; small doses intramuscularly thrice weekly for seven weeks; slight febrile reactions; recurrence in elbow joint; amputation of shoulder joint advised and finally performed. Death on February 1, 1909, listed as due to "phthisis, postoperative condition for sarcoma." (References 2, 54, 71a) 1⅔

2. (Calkins) *N. O.*, male, aged 20. Large polyhedral-cell sarcoma of thigh; football injury in September 1910; onset of sarcoma thereafter; more rapid growth, June 1, 1911; osteopath "massaged and kneaded it thoroughly"; exploratory incision mid-August 1911; hip-joint amputation August 28, 1911. Beginning September 10, 1911, toxins (Tracy XI) were given thrice weekly almost steadily for twelve months, then at monthly intervals for another six months; only mild reactions. Patient resumed work; lived on restricted vegetarian diet; subacute pleurisy of right lung, February 1913; death on October 7, 1913, apparently from pulmonary metastases. (41) 3

3. (Coley) *D. S.*, male, aged 27. Round-cell sarcoma of soft tissues over tibia; onset in March 1920; biopsy November 1920. Beginning November 11, 1920, toxins (Tracy XI) were given combined with radium pack (10,000 mch.); 17 injections in forty-five days; some febrile reactions to 103°–104° F.; several sinuses drained; *complete regression*; toxins continued twice weekly for two months. Patient gained weight; was symptom-free on January 19, 1921; pulmonary metastases, death on June 2, 1921. (41, 73, 81) 1½

4. (Coley) *M. B.*, male, aged 19. Fibrosarcoma or neurogenic sarcoma of soft tissues over radius, eroding bone; onset in September 1920. December 21, 1920, toxins started Tracy XI and Parke-Davis XIII given intramuscularly for three and a half months; circumference of tumor decreased 1¼ inches in first two weeks; exploratory incision January 5, 1921; 3 radium packs (31,400 mch.); disease controlled temporarily; later more radium given by Bloodgood without effect; axillary metastases April 1922; pulmonary metastases; death on May 1, 1923. (29, 35, 73) 2½

5. (Armstrong) *J. M. T.*, male, aged 80. Fibrosarcoma of muscles of forearm; date of onset not stated; preliminary x-ray therapy. April 24, 1920, toxins (Parke-Davis XIII) begun along with more x-ray therapy, and radium; 38 injections in sixty-five days; little or no reaction except when injected into central vascular part of tumor; tumor increased steadily in size; considerable pain; amputation June 29, 1920 (growth breaking down); 14 more injections, only 1 marked reaction; pulmonary metastases in December 1920; death in February 1921. (41, 81) 1+

6. (Coley) *M. S.*, male, aged 77. Diffuse round-cell sarcoma, possibly lymphosarcoma or liposarcoma, of chest wall, involving 9th and 10th ribs and pleura; onset in March 1921; exploratory operation November 11, 1921; tumor size of half an orange found; capsule torn, free hemorrhage, pneumothorax; 1 radium pack (8,159 mch.). Beginning November 19, 1921, toxins (XIII) started; seven doses given in about three weeks; *complete clinical regression*. Patient in excellent health July 7, 1922; another radium pack given (3,073 mch.); metastases developed in chest, abdomen and brain; death on September 18, 1923. (73, 81) 2½

7. (M. Clinic) *J. F. M.*, male, aged 17. Reticulum-cell sarcoma (Grade IV) involving plantar fascia and muscles of right foot in longitudinal arch region, without bone involvement. Incisional biopsy; amputation; toxins (XIV) given intravenously; 10 injections in about twelve days; reactions with fever to 104° F.; metastases in right groin and left scapula apparent one month after last dose; 6 more intravenous injections given; severe reactions; x-ray therapy to groin, scapular region, mediastinum, pelvis, left shoulder, and metastatic lesions (29

[4] Name of attending doctor.

Years traced

treatments in all); generalized metastases thereafter; further extensive x-ray therapy; blood transfusions; death one year after onset. (72) 1

8. (Coley) *A. G.*, male, aged 43. Twice recurrent spindle-cell sarcoma of right gluteal region; metastases to inguinal glands; onset in May 1894; growth size of fist removed at operation on July 8, 1895; recurrence; second operation in January 1896; another recurrence; mass 6 x 4 inches; considerable edema of entire limb; at third operation on May 27, 1896, entire mass was removed; inguinal metastases also removed. May 30, 1896, toxins (Buxton VI) begun; 17 injections in thirty-eight days; no marked reactions; considerable diminution in swelling of limb; pain decreased; patient able to walk; recurrence in April 1897; toxins resumed for three weeks; old cicatrix then excised; no evidence of disease; another recurrence; death. (73) 4

9. (Ansbach) *Mrs. L.*, aged 35. Fourth recurrence of spindle-cell sarcoma of muscles and fascia over sacroiliac joint; onset prior to June 1918; excision June 6, 1918; recurrent tumor removed September 11, 1918; thorough course of x-ray therapy; another local recurrence; third operation on August 12, 1919; radium and more x-ray therapy; fourth operation on January 29, 1920, left a gaping wound. Beginning February 20, 1920, toxins (Tracy XI) given intramuscularly intermittently for eight to ten weeks; no marked reactions; no effect; death in July 1920. (41, 81) 2

10. (Stewart) *R. G.*, male, aged 27. Recurrent round-cell sarcoma of psoas muscle involving 3-inch area of inner table of ilium: onset in April 1908; surgical removal August 15, 1908; recurrence; x-ray therapy every second day; erysipelas in November 1908 caused arrest of growth. Beginning February 25, 1909, toxins (Parke-Davis XII) given by subcutaneous injection; no reactions; with Tracy XI toxins only 1 decided reaction; total duration of therapy, four weeks; *complete regression* in three months. Patient gained 40 pounds; well for seven months; then rapid recurrence and death in 1910. (41, 102) 2

11. (Harmer) *G. P. C.*, male, aged 34. Thrice recurrent fibrosarcoma of the parotid; onset in summer of 1910; excision in October 1910; recurrence within two months; second operation on February 21, 1911; three doses of toxins (Parke-Davis XII) thereafter; no reactions; second recurrence six months later; paralysis of right side of face and right eyelids; third operation; more toxin therapy advised but not given, as patient felt he must return to work at once; third recurrence; toxins for two months in out-patient department; good reactions; tumor mass almost disappeared in six weeks; recurrence; no further treatment; death on May 15, 1912. (58, 71a) 1 9/12

12. (Coley) *I. A.*, male, aged 37. Fourth recurrence of neurogenic sarcoma of leg; onset, late 1914; primary tumor removed in 2 operations; recurrence; third operation; 23 x-ray treatments in 1919; no regression; deep radiation ulcer, 2½ by 3 inches; marked skin damage; fourth operation (biopsy only). Toxins (Tracy XI) begun on February 10, 1920; 31 injections given intramuscularly in forty-nine days; no marked reactions; radium pack treatments totalling 23,687 mch. given February to April 1920; biopsy on April 5, 1920, showed extensive fibrosis and some necrosis; disease involved tibia by April 5; amputation April 28, 1920; postoperatively, toxins were given for about eight months. Patient free from recurrence; in excellent health for twelve years; gained a lot of weight; then dieted (1932) and lost 10 pounds. At this time pulmonary symptoms developed with hemoptysis; in February 1933, coughed up piece of tumor tissue, found to be metastatic spindle-cell sarcoma; chest films showed a tumor involving the right upper lobe. Patient died suddenly on October 5, 1933, with hemoptysis. (73, 81) 19

13. (Coley) *F. R.*, male, aged 24. Twice recurrent neurogenic sarcoma of the right forearm (brachioplexus muscle); onset in August 1923; 2 operations followed

	Years traced
by prompt recurrences; second recurrence untreated; wound gaping. August 22, 1924, toxins (Parke-Davis XIII) started; only 7 intratumoral injections in sixteen days; tumor softened and decreased 1 inch in diameter after first dose; became more circumscribed; amputation on September 10, 1924; no further toxins; diffuse pulmonary metastases; death on January 31, 1927 (73)	4½
14. (Coley and Crandall) *Mrs. F. K.*, aged 40; recurrent extensive neurogenic sarcoma of left thigh; onset in December 1926; during second pregnancy in 1928, tumor increased much more rapidly; primary growth removed surgically when size of grapefruit; recurred (22 cm. in length); x-ray therapy. Beginning May 1, 1929, toxins (Parke-Davis XIII) given intravenously (5 doses); definite *regression*; radium packs (28,000 mch.); more toxins (8 intravenous injections); 50 per cent regression evident in four weeks; radium packs (45,000 mch.); toxins injected intramuscularly and sometimes intravenously; radiation ulcer 6 x 3 cm. on posterior left thigh; another radium pack; further x-ray therapy; slight improvement; inguinal, abdominal and lung metastases; death on March 30, 1930. (41, 73)	3¼

SUMMARY AND CONCLUSIONS (STUDIES XIII AND XIV)

An analysis of the factors involved in the treatment of inoperable and operable sarcoma of the soft tissues (excluding lymphosarcoma) with bacterial toxins (Coley toxins) has been made.

The most important factor influencing prognosis seems to be the type of toxin used. In some cases, only a weak preparation was available at the time the patient was treated. A factor of almost equal importance is the duration of treatment with the toxins, especially in the inoperable cases. There were a few successes with the use of a weak toxin, when it was administered persistently. In the majority of successful cases, the patients received injections every twenty-four to forty-eight hours during the early part of treatment.

In many of the cases considered to be failures, a great deal of x-ray or radium therapy had been administered, usually prior to toxin therapy.

The highest percentage of successful results occurred in patients who had a brisk reaction, chills and high fever (102°–105° F.) following an injection of toxin. Results were often satisfactory if injections were given into or near the growth. At the present time, administration of the toxins by intravenous injection, either alone or combined with a few injections into or near the growth when accessible, is the most effective method.

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APPENDIX

Analysis of Failures—67 Cases of Inoperable Sarcoma of the Soft Tissues Treated with Toxins (Series C)

Stage of the sarcoma when toxins were begun:

Primary inoperable: 15 cases (#3, 6, 17, 18, 19, 24, 27, 37, 38, 41, 46, 47, 51, 53 and 56).

Recurrent

1 seven times (#7);

3 five times (#1, 11 and 21);

5 three times (#4, 12, 45, 48 and 49);

19 once (#5, 10, 13, 14, 15, 16, 22, 26, 34, 36, 37, 41, 43, 44, 55, 59, 62, 65 and 67).

Multiple primary: 1 case (#30).

Metastases present: 22 cases (#1, 2, 3, 9, 10, 12, 13, 21, 28, 30, 33, 37, 42, 52, 54, 57, 59, 60, 61, 65, 66 and 67).

Terminal: 14 cases (#6, 9, 10, 14, 17, 20, 37, 40, 60, 63, 64, 65, 66 and 67).

Cachexia present or general condition poor: 11 cases (#15, 24, 25, 30, 34, 46, 52, 54, 55, 62 and 63).

Other treatment prior to toxins:

Radiation: 11 cases;

#40: x-ray therapy ineffective;

#46: x-ray therapy (twice weekly for 4½ months; tumor doubled in size);

#56: radium therapy (gold needles); diathermy, fulgurations (temporary benefit);

#57: x-ray therapy following excision did not prevent recurrence;

#58: x-ray therapy (46 treatments); recurrent tumor increased rapidly during treatment;

#59: x-ray therapy (no benefit);

#61: radium pack (8000 mch.), x-ray therapy (4 treatments) given twelve days after toxins; no decrease in size of tumor during this radiation;

#63: x-ray and radium therapy seemed to aggravate the condition;

#64: x-ray therapy (many courses), also radium therapy (5 treatments over 15-month period) did not prevent recurrence but destroyed eyelashes and brows;

#65: x-ray therapy (many courses to various metastatic areas totalling 32,024 r); patient's natural resistance to the neoplasm was remarkably high (died 8½ years after onset); an unusual case;

#66: x-ray therapy (4311 r) and radium therapy (1100 mch.) did not control the disease.

Surgery: 56 cases;

1—six operations: (#7);

3—five operations: (#1, 11 and 21);

2—"great many", "several operations": (#8 and 60);

7—three operations: (#20, 31, 33, 35, 45, 49 and 56);

10—two operations: (#4, 23, 25, 35, 40, 42, 59, 62, 63 and 67);

11—primary growth removed, usually completely; recurrence or metastases untreated or irradiated: (#2, 10, 26, 29, 34, 36, 43, 44, 55, 57 and 64);

7—incomplete removal of primary tumor: (#5, 13, 19, 31, 41, 48 and 65);

11—explorative and/or biopsy: (#6, 28, 30, 34, 37, 38, 46, 47, 50, 52 and 54);
3—amputation: (#28, 31 and 33);
1—electrolytic needles: (#24).

Other treatment during or after toxin therapy

Radiation: 9 cases;
#21: x-ray therapy for six weeks after 2 courses of toxins; complete regression;
#23: x-ray therapy (5 treatments about two weeks after toxins begun caused very rapid increase in growth;
#25: x-ray therapy thrice weekly during toxin therapy (often same day); very rapid improvement;
#28: x-ray therapy (30 treatments) five weeks after toxins;
#31: x-ray therapy (32 treatments) after ulcer healed, during toxin therapy;
#33: x-ray therapy, 5 weekly (begun one week after toxins given); little improvement;
#54: radium packs (5 treatments) between first and second course of toxins; marked improvement before and after radiation; then sudden death due to hemorrhage;
#55: x-ray therapy (3 treatments) before; radium packs (2 treatments) during toxin therapy;
#63: (x-ray therapy before); radium pack after (48,000 mch.); patient lost ground rapidly; much radiation sickness.

Surgery: 10 cases;
3—external carotids tied (#19, 21 and 23);
1—drainage established surgically (#20)
1—surgical removal (third operation); tumor much less vascular than before (#35);
2—incomplete removal (#1 and 9);
1—metastases; primary tumor removed at 2 operations two weeks after toxins (#9);
1—cicatrix removed after second course of toxins; no evidence of tumor (#13);
1—neck dissection, after toxins; patient died on operating table (#44).

Effects of toxin therapy

Complete regression: 8 cases;
#7: potent toxins four weeks; too rapid absorption of necrotic tumor caused persistent nausea;
#8: potent toxins 3½ years intermittently;
#12: potent toxins three months; resumed briefly later;
#13: potent toxins three months; resumed after further recurrence; tumor again regressed;
#22: potent toxins two months; resumed after recurrence;
#25: potent toxins, 3 courses, with x-ray therapy; later weak toxins; total one year;
#40: potent toxins, 3 courses; at first marked reactions; later no reactions (intramuscular);
#62: weaker product given daily at first intramuscularly and intratumorally; total seven months.

Incomplete regression: 29 cases;
#1, 2, 3 and 4 (marked), 6, 16, 18, 19, 26, 28, 30, 31, 33, 35, 37, 47, 48, 49, 52, 53, 54, 56, 57, 58, 59, 61, 63, 64 and 67.

Temporary arrest of growth: 9 cases;
#11, 21, 31, 32, 41, 43, 44, 46 and 65;

Marked relief of pain: 12 cases;
#13, 15, 23, 24, 26, 28, 37, 41, 53, 59, 64 and 67;

Cessation of hemorrhages: 1 case (#19);

Necrosis or sloughing of tumor: 9 cases;
#6, 12, 14, 15, 18, 19, 29, 30 and 34.

Little or no apparent benefit: 12 cases;

#5: only 5 doses;

#10: recurrence (11 by 15 inches); axillary involvement; toxin given intramuscularly remote from tumor;

#12: terminal; only 7 doses in the fifteen days before death.

#20: probable lung involvement; primary tumor 5 by 8 inches; toxins given only nine weeks (appetite remained excellent);

#27: only 2 doses; patient died after second dose given intra-abdominally;

#30: terminal; multiple primary tumors, metastases, arteriosclerosis and chronic nephritis; only 21 doses of weak product injected into tumors;

#33: weak product given six weeks, during x-ray therapy;

#37: 21 doses in forty-two days in a terminal case;

#38: only 2 doses; child, aged 2; died three days after second dose;

#55: weak product; very small doses intermittently after radium and x-ray therapy;

#60: weak product in terminal case; 6 small doses;

#66: terminal uterine tumor; multiple metastases (shock); 4 doses of toxins; little reaction; patient died three days after last dose.

Complications

Death during or soon after toxin therapy:

1—typhoid: #4;

5—sepsis: #5, 14, 26, 29 and 30 (all prior to 1901);

1—necrosis; collapse of tracheal wall: #53;

2—necrosis; hemorrhage: #45 and 54;

2—collapse (due to toxins?): #27 and 38;

1—radiation necrosis: #8;

1—uremia due to blocked ureters: #67.

Toxemia due to absorption of large amounts of necrotic tumor: 7 cases;

#5, 6, 14, 34, 40, 43 and 64. These cases suggest the need for establishing drainage surgicaliy, or for incomplete removal of the tumor.

Late survivals: 9 cases in which it would appear that the toxins prolonged the patient's life beyond the expected survival period:

Myxosarcoma (#8): about twenty-one years after toxins begun (twenty-two years after onset);

Tendon sheath (#12): about four years after toxins begun (five years after onset);

Thigh, groin (#13): about two years after toxins begun (four years after onset);

Uterus, broad ligament (#15): about six years after toxins begun (six and a half years after onset);

Thigh (#16): about two years after toxins begun (twenty-one years after onset);

Neck; metastases (#21): about twenty-one and a half years after toxins begun (fifteen years after onset);

Sarcoma of ovary (#22): four years after toxins begun (? years after onset);

Sarcoma of chest wall (#31): six years after toxins begun (nine years after onset);

Angiosarcoma of nasopharynx (#42): five years after toxins begun (ten years after onset).

LONGITUDINAL SOCIOPSYCHOLOGIC STUDY OF A RANDOMLY SELECTED GROUP OF INSTITUTIONALIZED VETERANS

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Within recent years the problem of aging has received increasing attention. This problem has been a particular concern of the Veterans Administration because of its responsibility in maintaining domiciliary facilities for veterans in the older age group. In order to augment the meager experimental data available, a study of the male members of the Domiciliary Service of the Veterans Administration Medical Center, Bay Pines, Florida, was made in the latter part of 1955.

The Domiciliary Service of this Medical Center began operation in 1933. For more than fifteen years its 680 beds for eligible male veterans and 50 for females have been virtually all occupied. Although some of the members are incapable of performing any type of useful work, others are able to perform various duties incident to the operation of the institution. In addition to the work activity program operated through members of adequate physical capacity, there are also available the recreational services typical of an institution for this age group.

PRESENTING PROBLEM

Particularly did it seem crucial to secure data which would provide answers to these questions:

1. Do the mental and personality traits of domiciliary members differ appreciably from those of men at large of similar age, education, vocational background and social status?
2. Is there evidence of any significant change in mental status or personality structure following prolonged sojourn in a VA domiciliary?
3. If there be significant differences in the mental and personality characteristics between domiciliary members as a group and the population at large, what are some of the implications arising therefrom?

PROCEDURE

The study comprised a group of 51 domiciliary members selected through a table of random numbers. The 51 members, embracing 7 per cent of the aggregate domiciliary population, were divided into three groups of 17 members each, in accordance with a triple sampling procedure. On the basis of history and psychologic test data the groups were found to be equivalent. In each case a complete medical, social, educational and vocational history was secured and a series of psychologic tests administered, namely:

1. A test of general intelligence.
2. A test of mental deterioration.
3. Projective personality tests, namely, Der Baum, Rorschach, and Szondi.

Two years later, in September 1957, the domiciliary experimental group was restudied

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through administration on five successive days of the Szondi Projective Personality Test, and the data compared with previous findings.

Normative data for controls came from three sources:

1. A normative group of 190 men of the same age group as the domiciliary sample, which was utilized by Wechsler for standardization of his Adult Intelligence Scale (1).
2. A European group of 4100 subjects ranging in age from 61 to 70, utilized in the standardization of the Szondi test (2).
3. A normative group utilized by Ames *et al.* (3) of Yale University, comprising 200 subjects, aged 70 to 90. In this study the normative group was divided into three categories designated: normal, pre-senile, and senile.

FINDINGS

Sociologic

The domiciliary sample population was very cosmopolitan, originating in 19 different states and 4 foreign countries.

The age distribution of the sample population was:

Under 50	2%
50–59	20%
60–64	33%
65–69	33%
Over 70	12%

Occupational status was as follows:

Professional and managerial—18% (compared to 8.2% in the general population)

Clerical and sales—29% (compared to 12% in the general population)

Service occupations—6% (same as in the general population)

Agricultural—12% (same as in the general population)

Skilled labor—20% (approximately equal to the 19–20% in the general population)

Unskilled labor—15% (compared to 8% in the general population).

From these data it may be noted that in the domiciliary sample the percentage of men formerly employed in the professional and managerial, clerical and sales, and unskilled labor fields was approximately twice the percentage employed in these categories in the general population. On the other hand, in the fields of agriculture, personal service, and skilled labor, the proportions were about the same for the two groups.

The educational level varied from third grade to completion of graduate work, the median educational level being eighth grade.

With respect to religion, the following percentages obtained: Catholic 25 per cent, Protestant 61 per cent, Jewish 2 per cent, and 12 per cent no preference.

Only 40 per cent reported membership in any type of organization; 44 per cent had less than one year military service; 30 per cent had been convicted one or more times in Manager's Court.

With respect to marital status, 39 per cent had never been married, in contrast to 8.8 per cent for men of the same age group in the normal population. The

number separated or divorced was approximately the same in our group and in the general population, being 26 per cent and 25 per cent, respectively. Thus it appears that whereas the divorce rate was approximately equal to that of the general population, the number of men in the domiciliary population who had never married was 4½ times greater. Only 45 per cent of those who married had progeny.

Medical

In addition to the physical afflictions characterizing virtually all of the domiciliary members, it is noteworthy that in the experimental group 48 per cent carried psychiatric diagnoses which were clinically established. These ranged from demonstrable psychotic states and epileptic convulsions through chronic brain syndromes, neuroses and mental deficiency, to manifest characterologic defects. In addition to this 48 per cent carrying psychiatric diagnoses, the psychologic testing revealed another 27 per cent who suffered from demonstrable psychiatric disorders such as psychoses in remission, mental deficiency, alcoholism, homosexuality, antisocial behavior and emotional instability. On the basis of these data, 75 per cent of the sample exhibited, either clinically or by other diagnostic procedure, syndromes of recognized psychiatric disorders.

Psychologic

1. *Mental status.* A comparison of the domiciliary sample with Wechsler's normal group revealed that the mean score of the domiciliary population sample surpassed Wechsler's group at all age levels with respect to such abstract factors as general information, comprehension, memory, computation and vocabulary. However, in manipulative and visual-motor tasks, Wechsler's normal group slightly surpassed the domiciliary group (Table 1).

A further question relating to mental status has to do with deterioration incident to institutionalization. Information bearing on this point was secured through administration of a standardized test for mental deterioration, namely, the Wechsler Memory Scale (Table 2). This test showed that of the 51 members in the domiciliary sample, 40 exhibited no trace of deterioration; 6, a significant degree of deterioration (10 to 20 per cent); and 5, a very significant degree (more than 20 per cent). Thus 78 per cent of our group manifested no deterioration, and among the other 22 per cent in every instance we were able to discover an organic basis for the deficit, such as severe epilepsy, chronic brain syndrome, central nervous system lues accompanied by hearing loss, and cerebral arteriosclerosis.

It was also noteworthy that when the cases of mental deficit based upon a demonstrable organic lesion were excluded, the members who had resided in the domiciliary for more than ten years displayed a significantly higher level of mental ability and less tendency toward deterioration than did the members who had been here for a lesser period. If we accept these findings gleaned from standardized tests of mental ability and deterioration, then we must conclude that residence at Bay Pines Domiciliary does not stultify nor depreciate in-

TABLE 1

A Comparison of the Mean and Standard Deviations on the Wechsler Adult Intelligence Scale of Wechsler's Normal Population Group with the Aggregate Bay Pines Domiciliary Group

Test or Subtest Item	Wechsler's Normal Group	Composite Bay Pines Group
Information	9.92*	10.49*
	3.43†	2.44†
Comprehension	9.56	10.29
	3.05	2.99
Arithmetic	9.28	9.73
	3.28	3.20
Similarities	8.72	9.08
	3.25	2.53
Digit span	8.05	9.39
	3.14	3.10
Vocabulary	10.14	10.75
	3.49	2.95
Digit symbol	6.06	4.83
	2.20	2.42
Picture completion	8.41	8.43
	2.64	2.97
Block design	7.77	7.35
	2.51	2.50
Picture arrangement	7.43	6.02
	2.34	2.57
Object assembly	7.66	7.24
	2.42	2.43
Aggregate verbal score	55.67	59.72
	16.27	13.04
Aggregate performance score	37.33	33.86
	10.14	10.28
Full scale score	93.0	93.59
	24.97	21.60

* Mean.
† Standard Deviation.

telligence and, further, that inadequate mental ability is no more prevalent in this domiciliary population than in the population at large.

2. *Personality structure.* If there be no essential difference between our domiciliary population sample and men at large with respect to mental status, what is the situation in regard to personality structure? In the Rorschach study of Ames *et al.*, the normative group was divided into normal, pre-senile and senile categories. Table 3 provides a comparison between the Bay Pines domiciliary group and the 3 groups embraced in Ames' study. It may be seen that for all the 15 determinants used in Ames' study, the Bay Pines group failed to attain a level equal to her normal group. On the contrary, the Bay Pines group closely approximated the Ames' pre-senile group. Moreover, with respect to the determinants presumed to measure initiative, creativity and originality, the Bay

TABLE 2

*Memory Quotients Achieved by the Bay Pines Domiciliary Group (51 Men) on the Wechsler Memory Scale, Form I, in 5 Age Categories**

Age Group (yrs.)				
40–49	50–59	60–64	65–69	Over 70
87	97	143	66	90
	116	125	77	77
	132	80	103	103
	106	99	87	96
	112	137	101	122
	106	86	120	94
	135	84	100	
	100	103	114	
	100	87	129	
	92	77	100	
	126	112	114	
		143	116	
		116	100	
		70	110	
		92	108	
		105	118	
			94	
Mean 87	111	103.5	103	97†

* MQ 90–100 = No deterioration.
MQ 80–89 = Significant deterioration.
MQ under 80 = Very significant deterioration.

† The relatively lower mean score of this group is an artifact resulting from the failure of the test to provide constants for ages over 64.

Pines group proved to be little better than the Ames' senile group. Curiously enough, that segment of the Bay Pines sample group comprising the 16 members who had been domiciled here for more than ten years gave an appreciably higher level of performance on the Rorschach test and hence showed a presumably better adjustment than did the remainder of the group. They did not, however, reach the level of Ames' normal group. These findings would indicate that the Bay Pines group was inferior to the normal population in such factors as conventional attitudes and orientation, adaptability, productivity, stamina, sociability, emotional control, and the ability to exercise initiative, creativity and originality. Through its deficiency in these essential traits, the Bay Pines group approximated the Ames pre-senile rather than the normal group. This leaves unanswered, however, the question of whether these men in the Bay Pines sample were prematurely pre-senile in vital personality traits or whether they had become fixated at this lower level in earlier life and were never able to surpass it. We shall pursue this point further.

3. *Implications of differences between populations.* A comparison of the Szondi test results for the Bay Pines sample with those for Szondi's normal group of

TABLE 3

A Comparison of Rorschach Determinants in Ames' Groups Versus the Aggregate Bay Pines Group (Mean Values)

	Ames' Groups*			Bay Pines Group (N—51)
	Normal (N—41)†	Pre-senile (N—140)	Senile (N—19)	
Total responses	25.90	15.70	13.50	16.92
F%	50.00	81.00	92.00	82.90
A%	46.00	55.00	40.00	56.10
No. of P	7.10	5.40	2.10	4.92
H + A	12.20	9.30	3.80	9.30
HD + AD	5.30	2.40	.70	2.50
Sum c	2.10	.70	.20	.70
M	3.30	1.60	.20	.50
FM + m	3.40	2.30	.30	.90
W	7.60	6.20	5.00	7.00
W%	36.00	43.00	46.00	50.60
D%	47.00	47.00	45.00	44.00
DD%	15.00	9.00	8.00	5.10
H + HD	6.00	3.00	.50	2.60
A + AD	11.40	8.60	4.00	9.20

* Ames *et al.* (ref. 3), pp. 34–35 (table 10) and p. 216 (table 42).
† N = No. of subjects.

4100 Europeans of equivalent age disclosed very significant differences. These differences are fundamental, as attested by the fact that other studies have shown marked similarities between Szondi's normal group and the normal subjects in our American culture (4). In Table 4 the following significant differences may be seen: The need to receive love, affection, devotion and attention was accumulated and unsatiated to an abnormal degree in the domiciliary sample, to a degree 1½ times greater than in Szondi's group. Moreover, the domiciliary group showed a level of dammed-up aggression twice as high as did Szondi's group. In contrast, the traits of altruism, subserviency to the needs of others, and cultural interests were 9 times as high in Szondi's subjects. Thus the domiciliary members are revealed as a group who suffer from continual frustration arising from a lack of devotion, affection and attention and who, at least partially as a result of this unsatiated need, tend to dam up feelings of frustration and hostility.

In ethical tendencies, there was no significant difference between the 2 groups. The desire to be recognized, to be the center of attraction, and gain esteem was 3 times as great in the normal group, whereas the desire for self-concealment and withdrawal was 1½ times greater in the Bay Pines group. Worldly ideals were developed in the normal control group to a degree 3 times greater than in the domiciliary population. In the domiciliary group, on the contrary, there was a tendency toward depreciation, disparagement and in some cases even debasement of worldly ideals. In some cases this approached the level of self-

TABLE 4

Respective Percentages of Subjects Yielding the 8 Factorial Responses on the Szondi Test in the Composite Bay Pines Group and in Szondi's Normal Population

	h	s	e	hy	k	p	d	m
Bay Pines Composite Group (51 subjects)								
+	89.4	61.9	18.8	5.4	3.9	23.1	24.7	29.8
−	1.1	11.7	36.8	68.6	76.8	40.3	33.3	33.3
±	1.9	3.5	11.3	5.4	5.8	11.8	4.7	9.4
0	7.4	22.7	32.9	20.3	13.3	24.7	37.2	27.4
Szondi's Normal Population Group (4100 subjects)								
+	67.0	31.0	19.0	18.0	11.0	10.0	39.0	53.0
−	9.0	37.0	31.0	45.0	56.0	66.0	18.0	21.0
±	13.0	14.0	14.0	13.0	16.0	8.0	8.0	14.0
0	11.0	18.0	36.0	24.0	17.0	16.0	35.0	12.0

Positive Signs (5)

h+ = Personal amorousness. This term comprises sensuous, sexual, undifferentiated amorousness. It includes a desire to be the sole object of love, tenderness and devotion from the amorous object.

s+ = Sadism. This need comprises masculine activity and aggression in the pursuit of vital goals and implies domination over other objects and persons.

e+ = Ethical behavior. This term comprises the trait of goodness, righteousness and conscientiousness. It implies the possession of ethical ideals.

hy+ = Exhibitionism. This tendency indicates the urge for esteem, recognition, vindication, approval and self-display. It implies the exhibition of the subject's behavior to the world.

k+ = Introjection. This term comprises internalization and incorporation of tangible and objective ideals which the ego has created. It implies an ego contraction.

Negative Signs (5)

h− = Love of humanity. This term encompasses an ideal, altruistic love of mankind in general; this is manifested through zeal and devotion toward philanthropic and reformatory activities designed for the amelioration of mankind.

s− = Masochism. This term indicates a need for feminine passivity, surrender and submission. It implies that the person is the recipient rather than the perpetrator of action involving persons or things.

e− = Unethical or evil behavior. This term denotes an accumulation of the gross affects of rage, anger, hatred, vengeance, jealousy and envy. It implies the incarnation of the evil within man.

hy− = Self-concealment. This term depicts the urge for self-concealment and modesty, and denotes the creation of a moral boundary of shamefacedness and loathsomeness.

k− = Negation. This term encompasses the tendency of disavowal, denial, renunciation, inhibition, repression and depreciation. It contemplates the demolition of tangible and projective ideals.

TABLE 4.—*Continued*

p+ = Inflation. This tendency comprises the creation of ego ideals and an obsession of the ego by ambitendencies. It is partially conscious and denotes ego expansion.	p.− = Projection. This reaction constitutes ejection of undesirable, unconscious impulses into the external world. It implies a lack of conscious awareness of the unconscious conflict.
d+ = Acquisition and variation. These involve a tendency to seek new objects of value and to take them into possession. They imply variation and change in the system of values.	d− = Constancy and steadfastness. These comprise the tendency to adhere loyally to the old amorous object with no disposition to seek substitute objects. They also imply an element of persistency in a scale of values and in attitudes.
m+ = Attachment and security. This tendency denotes a continuing attachment to the old amorous object and the further tendency to protect all acquisitions.	m− = Severance, detachment. This tendency comprises detachment from the world and the objects thereof. It implies instability and unpredictability.

destructive tendencies. The tendency toward suspiciousness, rationalization and projection of difficulty on others, however, was 1⅔ times greater in the control group. This indicates that, whereas the normal man tends to rationalize his errors and project his difficulty on others, the domiciliary member is more inclined to turn his conflicts inward and indulge in self-recrimination, obsessions of guilt, or some other type of self-punishment. This is often reflected in the self-sabotage inherent in the addiction practices, such as alcoholism, of many of the domiciliary members.

The domiciliary group showed more constancy in their emotional attachment, being 1¾ times more steadfast in their attachments than were Szondi's group. On the other hand, the domiciliary group showed themselves 1½ times more often estranged from people. These data indicate that the domiciliary member is more emotionally attached to his institution and clings to it with greater tenacity than characterizes the normal person's attachment to personal objects. Thus the institution provides the domiciliary member with an emotional anchor which is a recompense for his unsatiated affectional needs. More than this, the the institutional attachment is a very satisfactory repressive medium in defense against the outward expression of hostility which in its manifestation would cause the domiciliary member a great deal of difficulty.

The data relative to masculine-feminine personality attributes in the domiciliary sample indicated a preponderance of feminine traits in the ratio of 3 to 2, whereas a sample of normal men of this age group would never show a ratio higher than 1 to 1. Thus it is obvious that we are dealing with a very passive, subservient, dependent group. Such men encounter great difficulty in adjusting to the competitive society typical of contemporary America.

The lack of a statistically significant change in this test-retest group is demonstrated with respect to the personality factors measured by the Szondi test (as defined in the footnote to Table 4) by the chi-square values listed in Table 5.

TABLE 5

A Comparison of Chi-Square Values of the 8 Szondi Test Factors Relating to 40 Domiciliary Members Tested in 1955 and Retested in 1957

(Degrees of Freedom = 3)

+, −, ±, 0 Tendencies of Factors	x^2	P Values
h	1.224	>.70
s	4.352	>.20
e	.876	>.80
hy	2.436	>.30
k	1.156	>.70
p	1.272	>.70
d	2.008	>.50
m	3.424	>.30

Note that no change in the factorial tendencies attains the .05 level of confidence. It may therefore be concluded that the Domiciliary provides a remarkably stable environment despite the fact that ¾ of the group bear psychiatric diagnoses.

SUMMARY

A sample of 51 randomly selected subjects representing 7 per cent of the total male domiciliary group was studied by reviewing in each case the medical, social, educational and vocational history, and administering a series of psychologic tests to determine:

1. Whether the typical domiciliary member deviates in mental and personality traits from a man in the general population of similar age, education, vocational background and social status.
2. Whether there be evidence of change in mental status or personality structure following a prolonged sojourn in a VA domiciliary, and
3. Whether there be any implications arising from observed differences.

It was found that there is a significant difference between domiciliary members and the population at large in a number of socio-economic factors. For example, significantly fewer domiciliary members had ever been married, and of those who had married the greater proportion had never had progeny. The vocational distribution differed markedly from that of the general population. The educational level, however, showed the same wide range of distribution found in society at large.

With respect to medical status, it was noted that in 75 per cent of the domiciliary sample, in addition to any physical diagnosis, there was also a psychiatric diagnosis or demonstrable evidence of a psychiatric disorder. The latter ranged from fullblown psychoses through the gamut to characterologic disorders.

With respect to mental status, the domiciliary members demonstrated as high a level of general intelligence as did the population at large. The group of 16 residing in the institution for more than ten years manifested a higher degree of innate mental ability and a lesser degree of mental deterioration than did a segment in the general population of comparable age. Specifically, the domiciliary members demonstrated more capacity in those areas of mental functions in-

volving information, comprehension, computation, memory and vocabulary than in the areas involving manipulative and visual-motor activities. In the former area they surpassed the general population.

A special assay of deteriorative tendencies revealed that in 82 per cent there was no demonstrable deterioration, and that in the 18 per cent in whom deterioration occurred, it was due to a physical disorder. These data indicate that institutionalization in the Bay Pines Domiciliary per se resulted in no diminution of innate mental ability.

Personality was the area where the domiciliary members deviated most sharply from the general population. By comparison with the normative group of Ames *et al.* (which comprises the categories of normal, pre-senile and senile) the domiciliary sample fell far short of Ames' normal control group in such important factors as initiative, alertness, persistency, originality, flexibility, conventional release of accumulated affects, stamina, productivity and sociability. On the other hand the domiciliary group, upon the basis of Rorschach findings, were comparable in respect to virtually all the important personality characteristics with Ames' pre-senile group. Thus the Bay Pines sample showed a markedly greater tendency than did Ames' normal group toward stereotypy of thinking, rigidity of behavior, apathy, resignation and egocentricity. In the latter respect, the domiciliary group approached Ames' senile category.

The Bay Pines sample in comparison with Szondi's European population, a group which has been found in most respects to be comparable to the American population of similar age, showed a high degree of passivity, submission and tendency toward inactivity. There was an unfulfilled need for love, affection, devotion and attention on one hand and an accumulation of frustration and aggressive feelings on the other hand, far in excess of that prevailing in the control group. Experimental and control groups showed about the same degree of ethical tendencies, but the domiciliary group had a far greater tendency to repress the gross affects of anger, rage, hatred, vengeance, jealousy and envy. The domiciliary member's ability to accumulate and inhibit discharge of his emotions was brought about by his extreme seclusive tendencies which, in some cases, caused a withdrawal from personal contact to the point of tenuous reality contact or an actual reality break. The domiciliary group as a whole shunned popular attention and did not actively seek recognition. To a far greater degree than the control group, they exhibited negation, depreciation, disparagement and even debasement of worldly ideals which in some cases led to actual self-destructive tendencies. The domiciliary member in the sample group was found to be much more likely to turn his problems inward and repress them than to rationalize or project them on others, though in a few instances paranoid projection was noted.

In the realm of personal contacts the domiciliary members differed most markedly from the control group. They were found to be inconstant in their relationship to other persons but to be most steadfast in their adherence to the institutional ideal. These domiciliary subjects often can utilize the institution itself as an amorous object, even when they are incapable of emotional rapport with other persons. Results of projective tests uniformly indicated that the

men comprising the domiciliary sample were impoverished in their inner emotional and spiritual life. On the whole, they had long been personally inadequate. It is these inadequacies which account for the addictive tendencies, disciplinary problems and unstable relationships so prevalent in this group.

CONCLUSIONS

The following conclusions appear valid:

Men comprising a domiciliary population differ in many significant respects from a group of similar age, education, vocational background and social status in the general population.

Institutional life, as represented by Bay Pines VA Domiciliary, has no deleterious effect upon the individual member; on the contrary, he often makes a better adjustment in the controlled institutional environment than in any situation previously prevailing in the outside community.

Thus it appears that for men of the type residing in this institution, no more favorable solution to the problem of their case is available. They are persons who, even without physical ailments, would not be able to maintain more than a precarious and marginal level of self-sufficiency. Hence when, as in most instances, they suffer also from a physical ailment, adjustment outside an institution becomes for them an impossible goal. Over an extended period these men are unable to make a community adjustment. Therefore, it appears that some type of institution similar to the VA Domiciliary will always be necessary for their care. Moreover, with the increasing age of the veteran population, the need for such institutions will become not less, but greater.

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RADIOACTIVE FAT ABSORPTIVE PATTERNS IN THE GERIATRIC PATIENT*

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Many attempts have been made in the past to incriminate the aging process in the genesis of atherosclerosis. Indeed, for a long time, based on results of anatomic studies, it was universally held that the two were inevitable companions.

More recent thinking in this area has been concerned with a different approach, namely, the relation of atherosclerosis to lipid metabolism. Evidence is now rapidly accumulating which indicts some derangement thereof as a basic etiologic factor in this disease.

Fat metabolism, specifically in old age, has been inadequately studied. With the present availability of radioactive fat, a new tool can now be used to investigate the problem in a simple manner. This paper reports our current experiences in a group of geriatric subjects.

METHOD AND MATERIALS

The procedure has been described previously (1–3). Essentially it consists of the administration of a fat meal containing 25 microcuries of I^{131}-triolein in a total volume of 1 ml. per Kg. of body weight of peanut oil. Thereafter, venous blood samples are withdrawn periodically until a maximum radioactivity level has been reached, and again at the twenty-fourth hour. The radioactivity in each blood sample, as well as in the 24-hour urine, is determined and expressed as a percentage of the radioactivity in the initially ingested fat.

Fifty patients were studied whose ages ranged from 65 to 90 years. Half of the group had suffered a previous myocardial infarction. The others showed no evidence of any major disease and served as controls.

RESULTS

In 20 patients of the control group (80 per cent) there was a normal response (Table 1) to the ingestion of radioactive fat, and in 5 (20 per cent) an abnormal blood absorptive pattern was obtained (Table 2; Figs. 1 and 2). In 22 subjects of the "coronary" group (88 per cent) there was an abnormal response, and in the remaining 3 (12 per cent) the results were normal (Table 2; Fig. 3).

DISCUSSION

Becker, Meyer and Necheles (4) have previously studied the response of a group of 30 elderly patients to a fat meal, by performing chylomicron counts.

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TABLE 1

Criteria for Normal Radioactive Fat Tolerance Curve

	RA* Values (% ingested RA fat)		
	Whole blood	Lipid blood	Ratio LB/WB
Max. value (less than)	15	7.5	50
24-Hour value (less than)	5	0.5	50

* RA = radioactivity.

TABLE 2

Results of Radioactive Fat Tolerance Tests in Old Patients

	Number of Patients	Normal Results	Abnormal Results
Controls	25	20 (80%)	5 (20%)
Previous myocardial infarction	25	3 (12%)	22 (88%)

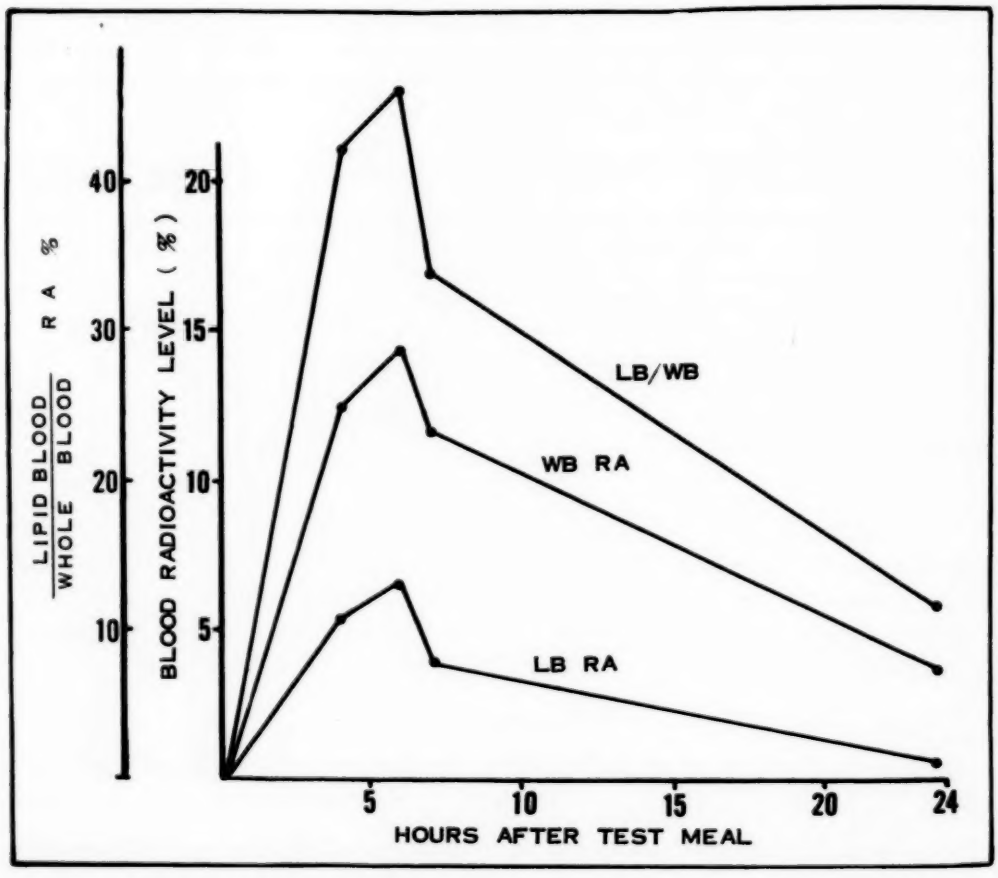

FIG. 1. Normal findings with radioactive fat tolerance test in an old patient with no evidence of atherosclerosis. (WB = whole blood; LB = lipid blood; RA = radioactivity.)

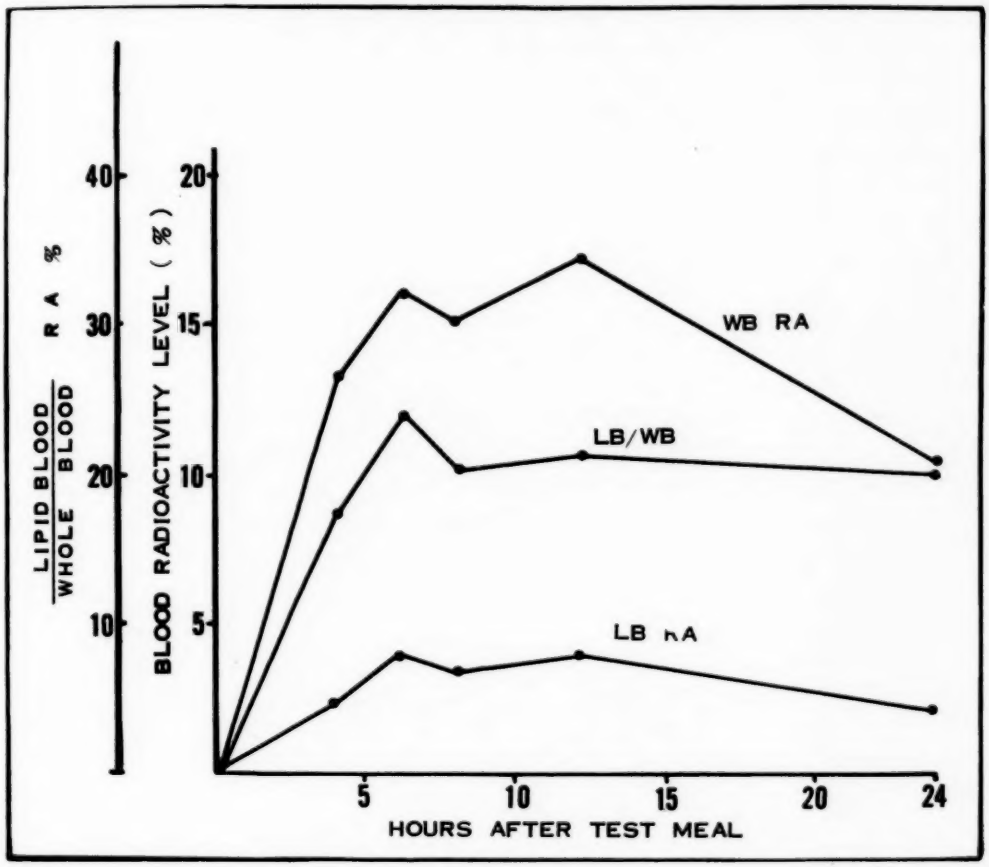

FIG. 2. Abnormal findings with radioactive fat test in an apparently healthy geriatric patient.

The counts in these patients were higher, the peaks were reached later, and clearing of the serum was more delayed than in a group of young controls. From these results they considered that there was a distinct decrease in the rate of fat absorption in aged subjects. It was also postulated that the prolonged hyperchylomicronemia which resulted after the fat meal might be related to the onset of arteriosclerosis.

Herzstein, Wang and Adlersberg likewise found an age difference in the response to the ingestion of a fat meal, characterized in old age by a prolonged elevation of the serum total lipid level (5). They suggested that this behavior might be related to a lowering of the basal metabolic rate or to a mechanism similar to that which affects glucose tolerance in the aged (6).

White, Ralston and Carne (7), on the other hand, found that age was less significant in affecting the height and duration of postprandial chylomicronemia than was activity during the test period.

However, the counting of chylomicrons or the chemical determination of serum lipids are not easy tasks and leave much to be desired.

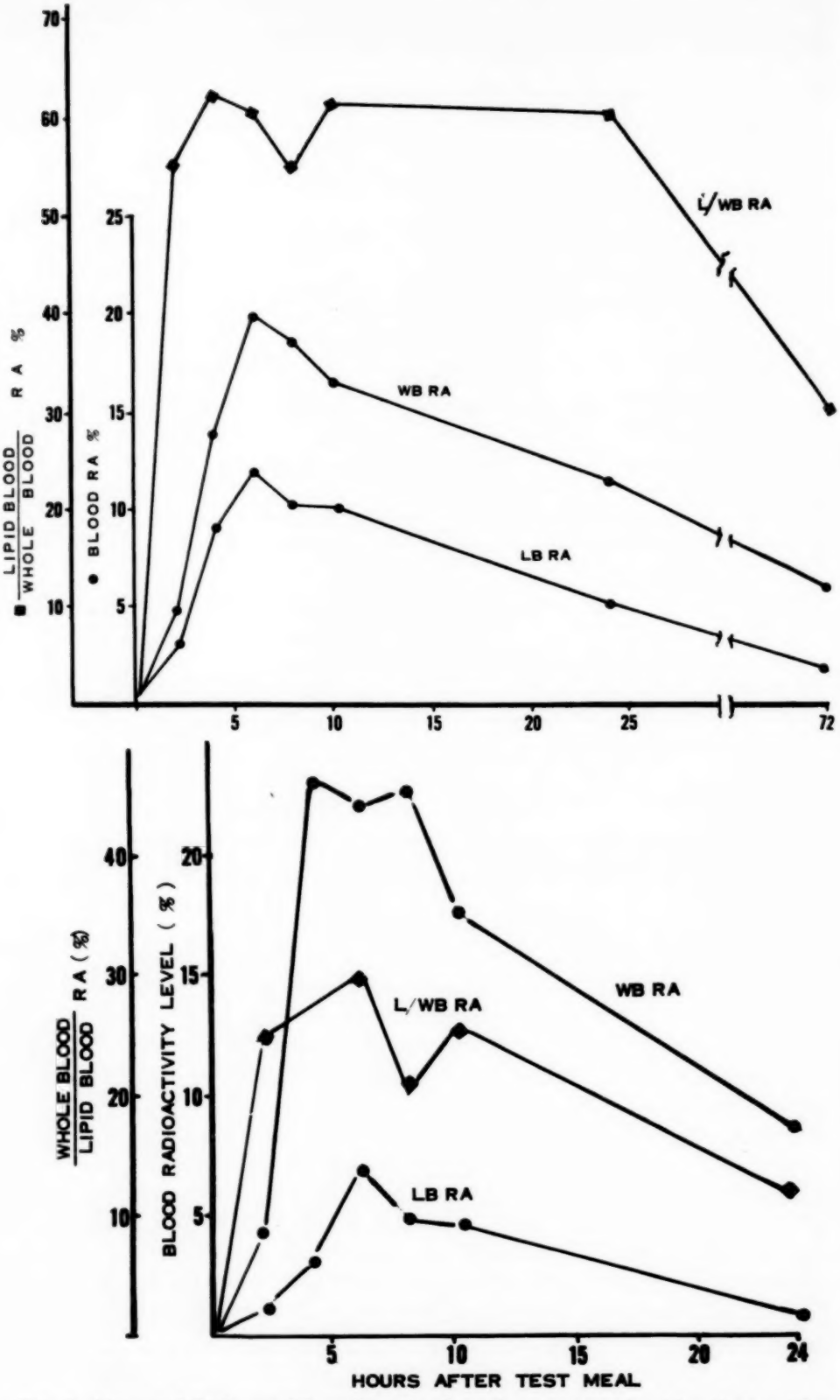

FIG. 3. Abnormal findings with radioactive fat tolerance tests in old patients with evidence of coronary artery disease.

The use of radioactive fat to study lipid metabolism was initiated by Thannhauser and Stanley in 1949 (8). Since then an increasing number of clinical reports have appeared, dealing mainly with the problem of malabsorption. We have increased the scope of this procedure by following the blood radioactivity levels over a 24-hour period and have included patients with coronary artery disease and/or hypercholesterolemia (2). The characteristic blood patterns observed in these patients suggested a relationship between atherosclerosis and a basic error in fat tolerance.

The present study is an extension of this work into the field of geriatrics. Impairment of fat tolerance, as demonstrated by elevated and prolonged postprandial radioactivity in the blood after ingestion of I^{131}-triolein, was mainly evident in those older patients who were atherosclerotic and had previously suffered a myocardial infarction. These results are similar to those already reported for younger subjects with coronary artery disease.

In the 5 "control" subjects whose I^{131}-fat tolerance was abnormal, a significant degree of atherosclerosis may have been present, even in the absence of clinical symptoms. The current results therefore strongly suggest that, contrary to previous reports, fat tolerance is not a function of age per se.

SUMMARY

Radioactive fat tolerance tests have been performed on 25 apparently healthy geriatric patients and on 25 who had previously suffered a myocardial infarction. Fat tolerance in general was similar to that in younger subjects with comparable disease states.

It is postulated that age per se does not influence fat tolerance. Impairment may be indicative of some abnormality in lipid metabolism which could well have preceded the attainment of old age.

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Abstracts of Current Literature

THE VASCULOCARDIAC SYNDROME OF METASTATIC CARCINOID.

Bean, W. B., and Funk, D. *A.M.A. Arch. Int. Med.* **103:** 189 (Feb.) 1959.

A case is reported of the vasculocardiac syndrome caused by hyperserotoninemia produced by a metastatic carcinoid tumor in the liver. The primary lesion was situated in the upper ileum. Results of the Undenfried test for 5-hydroxyindolacetic acid in the urine, which is specific in the diagnosis of metastatic carcinoid, were strongly positive, and the 24-hour specimen of urine contained grossly abnormal amounts. The tumor was found to contain 88 micrograms of serotonin per gram. Analysis of blood platelets for serotonin yielded values two to four times normal. There were no abnormalities of blood coagulation. The patient had a transient waxing and waning of erythema in blotchy patches around the face and neck that became spectacular with time. Flushing could be elicited by pressure upon the liver. Dark, flat angiomas appeared, and there were numerous networks of fine telangiectatic vessels disseminated over the skin. The administration of serotonin antagonists produced no change in the signs or symptoms. Considering the vasomotor, angiomatous, bronchoconstrictor, hyperperistaltic, and cardiospastic manifestations of the syndrome, it appears that the physiologic disorder is smooth-muscle spasm which is strongest in the blood vessels, skin, heart valve and bowel. Repeated exposure to serotonin over a long period leads to disorganization of these structures and their function suffers because of high serotonin levels.

RUPTURED ABDOMINAL ANEURYSM IN ELDERLY PATIENTS: REPORT OF A CASE WITH RECOVERY.

Boyd, D. P. *Lahey Clinic Bull.* **11:** 34 (Oct.–Dec.) 1958.

When pain appears in a case of abdominal aneurysm, rupture may follow at any time. The case reported illustrates the feasibility of major surgical procedures regardless of the age of the patient, provided other organs are reasonably normal. The occurrence of complications has proved to be related to the functional status of other organ systems rather then to the age of the patient. In the case presented, the patient was an 83-year-old man. The aneurysm was removed following rupture and continuity restored with an Orlon prosthesis.

HYDROCHLOROTHIAZIDE IN THE TREATMENT OF CONGESTIVE HEART FAILURE.

Brest, A. N., and Likoff, W. *Am. J. Cardiol.* **3:** 144 (Feb.) 1959.

Among the 20 patients in this study with congestive heart failure, 5 had not previously received diuretics (Class I). Three cases (Class II) had, and 12 (Class III) had not, been controlled with diuretic therapy. Class I subjects received 50 mg. of hydrochlorothiazide once or twice daily, Class II subjects the same dosage twice daily, and Class III subjects 50 mg. three times daily. Congestive failure was completely controlled in 16 patients as follows: 4, 3, and 9 in Classes I, II, and III, respectively. Two patients in Class III improved, but the congestive failure could not be completely controlled. One patient could not tolerate hydrochlorothiazide because of severe nausea, so that the drug had to be discontinued. One other patient failed to have a diuretic response. In all subjects a mild hypochloremia developed that caused no clinical signs or symptoms. No significant changes occurred in the serum

potassium or sodium levels. No deleterious effects upon either the blood or renal function could be detected. Nausea was the only side-effect and occurred in a total of 3 patients, but in 2 of them did not prevent continuation of medication. Investigation is continuing to determine the minimal effective dose, long-term follow-up results, and comparative effect of this drug with other diuretic agents.

PROTÉINES ET LIPOPROTÉINES DANS LE DIABÈTE. (PROTEINS AND LIPOPROTEINS IN DIABETES).

Castiglioni, C. A.; Rocca, F. F., and Garbino, C. Y. *Presse méd.* **66:** 1750, 1958; through Ciba Literature Review **4:** 43, 1959.

The fact that late complications frequently occur in diabetes even though carbohydrate metabolism appears to have been correctly regulated with the aid of insulin suggests that this disease involves a more radical metabolic disorder affecting fats and proteins as well. The change in fat and protein metabolism is not a consequence of the disturbance in carbohydrate metabolism, but a primary defect connected with the diabetes. The authors made the following observations in 80 nonselected diabetic patients, 44 of whom were over 60 years of age: the blood albumin level was reduced, while the quantity of globulin was above normal, with the result that the protein quotient was inverted. Cholesterol and beta-lipoprotein levels were elevated. The sedimentation rate was accelerated in 80 per cent of the cases. There were no significant differences between the various age categories, and the existence or nonexistence of vascular complications was likewise of little importance. The duration of the diabetes and the quality of the regulation (with insulin or D-860) also appeared to have no effect, except with regard to the beta-lipoproteins which tended to increase in quantity when the disease was of fairly long duration, or treatment inadequate.

PULMONARY TUBERCULOSIS ASSOCIATED WITH CARCINOMA OF THE LUNG.

Christoforidis, A. J., and Browning, R. H. *A.M.A. Arch. Int. Med.* **103:** 231 (Feb.) 1959.

Pulmonary tuberculosis and bronchogenic carcinoma occur together more frequently than has been recognized. This is because the distribution of active pulmonary tuberculosis is shifting to older age groups, and because carcinoma of the lungs is increasing in frequency and constitutes a higher percentage of all malignant tumors. Ten case reports illustrate the concomitant existence of these two diseases. In 6 of the patients, the first manifestation of carcinoma was unilateral hilar lymph-node enlargement. This important sign is usually present before symptoms appear and often is overlooked. Detection is the problem, and accurate measurement essential. Once hilar adenopathy has been detected, more accurate diagnostic procedures can be carried out. A hilus greater than 5.5 cm. in transverse diameter is suspicious, and any above 7.0 cm. should be considered abnormal and evaluated further. A difference of more than 2 cm. between the two hila should also be considered abnormal. The first manifestation of carcinoma may sometimes be a pulmonary infiltrate near to or remote from the tuberculous lesions. The persistence or increase of such an infiltrate despite improvement in the tuberculous disease should suggest the presence of a second disease, and primary consideration given to malignancy. Other signs and symptoms in tuberculous patients that require careful investigation to rule out bronchogenic carcinoma include a unilateral wheeze which has not previously been present, the occurrence of hemoptysis or blood-streaked sputum, weight loss, and anemia. A study of the roentgenograms of tuberculous patients may permit such questions as these to be answered: Is the new infiltration associated with ipsilateral hilar adenopathy? Is it increasing in size despite treatment? Does it contain carcinoma of the laminated or the so-called popcorn type, both of which are unlikely to be associated with a malignant lesion? Is metastatic bone involvement present? Has any new cavity appeared? Is the new lesion located anteriorally?

A PRELIMINARY STUDY OF IPRONIAZID IN RHEUMATOID ARTHRITIS.

Coke, H.; Furber, S. E., and Kerr-Taylor, H. *Rheumatism* **15:** 2 (Jan.) 1959.

Twenty-six ambulant patients who had severe rheumatoid arthritis with excessive weight loss and muscle wasting or in whom depression was a major feature, 3 patients with osteoarthritis and marked depression, 1 with ankylosing spondylitis, and 2 with a depressive psychosis, were treated with iproniazid. Fourteen patients were treated for only two weeks because of the occurrence of side-effects (12 patients) or lack of benefit (2 patients). The other 18 were treated and observed for periods of two months to one year. No significant effect upon arthritis was obtained unless a dosage of 150 mg. per day was used. At this dosage level, the drug is potentially toxic. The immediate toxic effects were attributable to hyperexcitability of the nervous system and to edema. Late toxic effects occurred in 2 patients; they were serious only in 1 patient who lost consciousness and collapsed after three months' treatment. The benefits in the patients treated over the longer period consisted of the relief of depression with an elevation in mood, gain in weight, and improved functional capacity. It is concluded that iproniazid provides substantial benefit in the management of certain selected cases of rheumatoid arthritis with psychic disturbances. However, there is no evidence of improvement in the inflammatory disease process during the administration of iproniazid.

THE MANAGEMENT OF CONGESTIVE HEART FAILURE WITH A FREE SALT INTAKE.

Eskwith, I. S. *Am. J. Cardiol.* **13:** 184 (Feb.) 1959.

A regimen consisting of digitalization, the injection of a mercurial diuretic if necessary, the administration of chlorothiazide in a dosage of 0.5 Gm. three times daily for one week and then 0.5 Gm. twice daily for maintenance, plus a free salt intake was used in the management of 23 patients of average age 61 years with heart disease of diverse etiologies. The average period of treatment was twenty months (range three to eighty-four months). Complete absence of dyspnea or edema or both and the resumption of relatively full activity was achieved in 19 patients. Incomplete relief of edema or dyspnea, or the passage of two years without an episode of decompensation was obtained in 3 patients. One patient received no benefit and had two episodes of decompensation while being treated with a supposedly adequate diuretic regimen. No evidence of renal insufficiency or of progression of existing insufficiency could be detected in the 15 patients in whom blood urea nitrogen determinations were made. No renal damage became apparent during the period of observation. This plan of management is based upon the belief that sodium restriction is unnecessary with the availability of effective diuretic agents. It allows the patient greater freedom in dietary intake. It is also postulated that it will eliminate some of the electrolyte disturbances previously observed in congestive heart failure.

PALLIATIVE TREATMENT OF BENIGN PROSTATIC HYPERTROPHY. VALUE OF GLYCINE-ALANINE-GLUTAMIC ACID COMBINATION.

Feinblatt, H. M., and Gant, J. C. *Southwest. Med.* **40:** 109 (Feb.) 1959.

Forty men of average age 60 years with benign prostatic hypertrophy received a preparation containing glycine, alanine, and glutamic acid three times daily after meals for three months. The results were compared with those during a two-month control period when the same patients received placebo medication. The prostate was reduced in size by this therapy in 37 patients, and to normal size in 13 of them. Nocturia was relieved to some extent in 38 patients, and completely in 29 of them. Also relieved were urgency of urination in 32, frequency in 29, discomfort in 28, and delayed micturition in 28 patients. The disappearance of pitting edema in the legs and various parts of the body was part of the benefit. No comparable improvement could be observed during the control period. No adverse reactions occurred. The effects are assumed to be due to an anti-edema (diuretic) action which re-

lieves the edema affecting the prostate gland and surrounding perineal tissues. A metabolic effect of the amino acids may be a factor. It is recommended that prostatic hypertrophy be treated conservatively except in emergency situations, particularly since it is present to a certain extent in all elderly men and should probably be regarded as a normal concomitant of old age. The glycine-alanine-glutamic acid mixture offers palliative therapy and is worthy of further investigation.

LABORATORY AND CLINICAL OBSERVATIONS ON CHLORAZANIL, A NONMERCURIAL ORALLY EFFECTIVE DIURETIC AGENT.

Ford, R. V.; Rochelle, J. B.; Bullock, A. C.; Spurr, C. L.; Handley, C., and Moyer, J. H. *Am. J. Cardiol.* **3:** 148 (Feb.) 1959.

In dogs, the intravenous administration of chlorazanil (Daquin) was followed by a significant increase in sodium and water excretion. The percentile increase in excretion of water was greater than that with natriuretic agents of comparable potency. The effective dosage range in man lies between 300 and 600 mg. per day. The onset of action is within two hours and its duration approximately eighteen hours. Its potency is approximately half that of Mercuhydrin; 600 mg. orally produces an increase in sodium excretion equivalent to that observed following the injection of 1 ml. of Mercuhydrin imtramuscularly. Other potency comparisons show chlorazanil to be more potent than Diamox, equipotent with Neohydrin, but less potent than Mictine and Diuril when each is given orally in a single dose. However, if diuretic potency is calculated on changes (acute) in urine volume, chlorazanil orally is more potent than is Mercuhydrin administered parenterally. Aminophylline administerd orally concomitantly with chlorazanil had no effect upon its potency. Chronic daily administration of chlorazanil is moderately and continuously effective, but doses greater than 300 mg. may produce evidence of a decrease in glomerular filtration rate. Side-effects consisted of anorexia, occasional vomiting, potentiation of ganglionic blockade, and generalized weakness. These were seen more frequently with the larger dosage. The mechanism of action of chlorazanil differs from that of chlorothiazide, mercurials, and carbonic anhydrase inhibitors. Following the administration of 600 mg. as a single oral dose, there is a consistent and extensive increase in the excretion of sodium but this is not completely paralleled by chloride. The excretion of bicarbonate is increased in a proportion of approximately 10 to 25 per cent that of chloride, but this effect is not seen consistently. Potassium is sometimes increased. The pH of the urine is slightly increased by the drug; titratable acidity, phosphate, and ammonia excretion are slightly depressed at the peak of its action.

CONTROLLED STUDIES ON THE EFFICACY OF BILATERAL INTERNAL MAMMARY ARTERY LIGATION IN PATIENTS WITH ANGINA PECTORIS.

Fremont, R. E.; Klopstock, R., and Glass, P. *Angiology* **10:** 20 (Feb.) 1959.

Pilot studies were carried out in a small group of patients with angina pectoris who were subjected to ligation of both internal mammary arteries in the second intercostal space. Both sham operations and serial exercise electrocardiography were utilized in some of the patients in addition to rest electrocardiograms and ballistocardiograms. Pitfalls in the evaluation of patients before and after surgery are numerous both as regards symptoms and, to a lesser extent, objective tests. Internal mammary artery ligation, like all other types of coronary surgery, has a considerable psychologic component which accounts for the rapid subjective improvement in most patients, regardless of the severity of the disease. Prolonged subjective improvement was noted only in those patients who had a mild form of the disease. Objective improvement as manifested by improved or normalized exercise electrocardiographic response was similarly limited to those with the mildest forms of the disease. The use of ligation of both internal mammary arteries for the treatment of coronary disease requires further careful study based on a large number of patients and employing objective

data. These should include sham procedures and exercise electrocardiography. (From authors' summary and conclusions.)

SOME UNUSUAL CASES OF CEREBRAL TUBERCULOSIS.

King, A. B. *Bull. Johns Hopkins Hosp.* **104:** 75 (Feb.) 1959.

The case histories of 4 patients aged 47, 65, 65 and 70 years, respectively, illustrate that the possibility of all forms of tuberculosis must be considered in geriatric patients, even when "negative" roentgenograms of the chest are obtained. Such negative findings delayed diagnosis in these patients. The primary lesions were relatively silent, both in producing symptoms of intracranial hypertension and in local neurologic deficits. By the time tuberculous meningitis was suspected, the disease was well advanced. Medical therapy instituted at this time was of little or no benefit. In each patient one or more cerebral tuberculomas were found. One case was unusual in that a 65-year-old man died of a rapidly fulminating tuberculous meningitis. In another, the onset of tuberculous meningitis was slow and insidious. The disease was not suspected in this 70-year-old man because of his age. In a third patient, cerebral symptoms masked the findings that might have led to an earlier diagnosis. None of the tuberculomas was removed surgically, although this is now the treatment of choice. Had they been, it is possible that medical therapy might have proved more successful.

GERIATRIC OPHTHALMOLOGY.

King, J. H., Jr. *South. M. J.* **51:** 236, 1958; through Excerpta Med. (Gerontol. & Geriatrics) **1:** 204, 1958.

Physiology and pathology of ocular senescence are described. The importance of vague visual complaints is pointed out; they may be warning signs of impending danger. Thus, failing vision in the absence of ocular pathology may be due to changes in the visual centers; in the basilar or carotid systems a terminal artery may have become occluded and one should be alert for symptoms preceding a stroke. A temporary blackout of vision combined with forewarning neurologic signs may precede thrombosis of the basilar artery. Thrombosis of the internal carotid may be preceded by cephalea and recurrent transient blindness of one eye. Thus recurrent ocular symptoms may be followed by aphasia and hemiplegia. Headache in the temples or occiput, perhaps accompanied by visual complaints, may point to temporal arteritis. If the inflammation goes on, the arteria centralis retinae is apt to become involved with resulting amaurosis. The early use of corticosteroids may repress the inflammation. Recurrent dimming of vision without an apparent reason may point to impending occlusion of retinal veins. Anticoagulant treatment should be started prophylactically. Changes in the fundus due to retinal vascular disease are described. It is pointed out that metastatic carcinoma of the choroid, usually secondary to mammary or pulmonary carcinoma, has a greater frequency than was thought formerly. Thus prior to radical surgery a thorough ophthalmoscopic examination should be made. Statistics of causes of blindness are given and the necessity of prophylaxis is stressed.

ALDOSTERONE IN CONGESTIVE HEART FAILURE.

Lenzi, F.; Caniggia, A.; DiPerri, T.; Guideri, R., and Ravenni, G. *Acta med. scandinav.* **163:** 329, 1959, Fasc. 4.

High values of aldosterone—8.5 to 160 gamma per twenty-four hours—were found in the urine of patients with congestive heart failure. Values in normal subjects did not exceed 10 gamma. When 13 patients with congestive heart failure were fasted for five to six days, aldosteronuria progressively decreased, while urinary output and sodium elimination increased. The patients recovered during this regimen, sometimes without cardiotonic therapy; edema, cyanosis and dyspnea disappeared, the heart rate diminished, the venous pressure returned to normal values, diuresis was activated with an increase in the glomer-

ular filtrate, and the electrocardiogram showed shortening of the electrical systole. Patients with congestive heart failure were found to display greater aldosterone excretion in the vertical position than when lying prone. Experiments in normal subjects confirmed the existence of a night-day rhythm in aldosteronuria. The rhythm was noted also in cardiac patients. The patients chosen had marked nocturia: during the night, the total urinary aldosterone content decreased with respect to the daytime content despite the marked increase in water and salt excretion. In normal subjects, the administration of sodium chloride led to a noticeable reduction in aldosteronuria, but in the majority of patients with congestive heart failure, aldosteronuria increased when an intravenous injection of sodium chloride was given. The authors consider cellular hypoxia, with the cells acquiring sodium ions so that they take up water and become swollen, to be the basis of hyperaldosteronism in congestive heart failure. The various observations are discussed in the light of this theory.

STATUS OF THE THYROID GLAND AFTER AGE 50.

McGavack, T. H., and Seegers, W. *Metabolism* **8:** 136 (March) 1959.

The status of the thyroid gland was studied in 610 subjects, 501 of whom were over 60 years of age. There is a steady decrease in the size of the thyroid until the age of 80 years, with no significant change thereafter up to 101 years. This change is associated with atrophy and fibrolymphocytic replacement of the parenchyma and a decreased blood supply. Nontoxic nodular goiter was the most commonly seen abnormality of the thyroid, being present in 4.2 per cent of the subjects over age 60 years. Instances of hyperthyroidism, hypothyroidism, and cancer were also observed. With age there was a gradual decrease in the basal metabolic rate and the thyroidal uptake of radioiodine, but both these functions appeared to "level off" between 75 and 85 years of age. Values for serum cholesterol and serum protein-bound iodine concentration varied widely from individual to individual, but no definite correlations could be established between such values and the physical status of the gland or other parameters of thyroid function. In 75 per cent of the subjects 60 years of age or older who had a very low initial thyroidal uptake of I^{131}, the response to a single dose of thyroid-stimulating hormone was normal. A definite association between abnormal thyroid function and female genital-tract disease could be established. (From authors' summary.)

FRACTURES OF THE PELVIS OCCURRING IN SENILE CONVULSIONS.

McGoey, P. F. *Canad. M.A.J.* **80:** 372 (March 1) 1959.

Four similar vertical oblique fractures through the acetabula in 3 elderly men occurred following spontaneous convulsions. It is suggested that convulsions should be suspected whenever such a fracture is seen in the absence of external bruising.

INSERTIONSTENDINOOSTEOPATHIEN IM BEREICH DER HALSWIRBELSÄULE. (INSERTIONAL TENDINO-OSTEOPATHIES IN THE CERVICAL VERTEBRAL REGION).

Manz, A. *Zentralbl. allg. Path. u path. Anat.* **97:** 71, 1957; through Excerpta Med. (Gerontol. & Geriatrics) **2:** 12, 1959.

The lower two-thirds of the cervical vertebral column with the surrounding soft parts were microscopically examined in 5 elderly people whose deaths were not related to the spinal column, which showed no external anomalies. The following changes were found: 1) calcium deposits exclusively in ligaments and tendons, in particular close to the place of insertion of the bone; 2) less often than these parossal calcium deposits, cracks and tears were found in ligaments and tendons, also usually parossally; 3) "Umbau" of the cortical layer, for instance, by displacement of the edge of the bone in the direction of traction of the tendon. The cause is chiefly mechanical stress, complicated by degenerative changes due to old age.

ANGINA PECTORIS. ITS ALLEVIATION WITH CHLOROTHIAZIDE.

Marshall, F. A. *Am. J. Cardiol.* **3:** 180 (Feb.) 1959.

The beneficial effects of chlorothiazide were discovered during its investigation as a diuretic agent. Chlorothiazide in a dosage of 0.5 Gm. twice daily relieved the pain of angina pectoris in 11 patients, and partially relieved pain in 14 others. The response commenced within two hours and lasted for six to eight or twelve hours. A dosage of 1 Gm. daily was continued for ten days, and thereafter as the patients needed it for the relief of pain or until diuresis clinically had ceased. Four patients showed no evidence of diuresis but this did not prevent their obtaining benefit from the drug. As the diuretic effect in the remainder waned, so also did the relief from angina. From this study, chlorothiazide appears to be effective in sparing nitroglycerine.

LA RESERPINA NEL TRATTAMENTO COLINERGICO DEL DIABETE MELLITO IN MALATI ARTERIOSCLEROTICI. (RESERPINE IN THE MANAGEMENT OF DIABETES MELLITUS IN ARTERIOSCLEROTIC PATIENTS).

Nadel, M. B. J. *Giorn. gerontol.* **6:** 107, 1958; through Ciba Literature Review **4:** 44, 1959.

In diabetic patients with arteriosclerosis, with and without hypertension, the administration of Serpasil releases serotonin. In Nadel's opinion, this effect not only brings about a fall in the elevated pressure, but also appreciably damps down pathologic autonomic nervous symptoms, nervousness, and excitability. This vagotonic effect is produced without the patient feeling drowsy during the day. Serpasil alone is able to lower the blood sugar level in mild cases. The drug makes it possible to reduce the daily requirement of insulin, to break down insulin resistance, and to diminish the incidence of hypersensitivity reactions. By releasing serotonin in the body, Serpasil has a beneficial effect on polyuria in elderly diabetic subjects. Acidosis and polydipsia also are considerably improved. To arteriosclerotic patients, aged 58 to 72 years, and with more or less severe diabetes, Serpasil was administered initially in doses of 0.1 mg. orally three times daily. The dosage was increased progressively for six to seven days until the optimum dose was found which proved, in exceptional cases, to be as much as 1.75 mg. daily. This optimum dosage was given until the twelfth day. Following a rest period of one week, treatment was resumed along the same lines, the second course being somewhat longer.

REVERSAL OF INTRACTABLE CARDIAC EDEMA WITH PREDNISONE.

Newman, D. A. *New York State J. Med.* **59:** 625 (Feb. 15) 1959.

In 8 cases of intractable cardiac edema, the administration of prednisone re-established the responsiveness of the patient to diuretic agents. These were patients with arteriosclerotic heart disease. Among them 6 had severe hypertension, 5 had had one or more myocardial infarction, 2 had aortic regurgitation, 1 had pericardial calcification and constriction, and 1 had diabetic glomerulosclerosis and the nephrotic syndrome. All had been under treatment for congestive heart failure for two or more years. All standard measures of therapy including the use of chlorothiazide and induced hyperchloremic acidosis had been exhausted without improvement in their condition. The outlook was hopeless prior to the administration of prednisone. One patient treated with ACTH failed to respond. One additional patient who received prednisone died from a cerebrovascular accident before diuresis could be established. In 5 of the patients successfully treated with prednisone there has been good compensation for periods of nine to twenty-eight months. The 3 patients in the series who died had periods of satisfactory compensation for nine months to two years following reversal of their intractable failure. Death was caused by discontinuation of prednisone by the patient, acute myocardial infarction, and by bronchopneumonia in 1 patient each. Initially, prednisone was administered in dosages of 2.5 mg. per day. This was

increased carefully to 15 to 20 mg. per day for four to five days, and then the dosage gradually decreased in accordance with the patient's response to a mercurial drug given after priming with prednisone. The maintenance level averaged 5 mg. per day. The minimal dose that would exert a sodium-excreting effect rather than a sodium-retaining effect had to be determined empirically in each patient. Each of the 8 patients again became responsive not only to mercurials (in smaller dosage than previously) but to Diamox, chlorothiazide, and Neohydrin. This responsiveness was maintained as long as small doses of prednisone were continued, except in patients in whom an intercurrent complicating disease developed. Moderate weight gain occurred during the first four to five days of prednisone administration. This was followed by moderate diuresis on approximately the fifth day. Thereafter, a brisk diuresis with a weight loss of 8 to 10 pounds occurred when a mercurial drug was given. The diruesis was characterized by a greater output of water than of chloride. Prednisone seemed to be particularly effective in the 3 patients with bronchopulmonary disease. The usual contraindications to prednisone were accepted as calculated risks in these patients and appropriate counter-measures employed. Prednisone appears to promote redistribution of electrolytes and water between the various fluid compartments, bringing about a backshift of sodium into the extracellular fluid space and making it presentable again to the kidney tubules for reabsorption. Diuretic drugs are then able once again to block its reabsorption. This is a view supported by other recent publications.

Addendum: Since this report was prepared, intractable failure in 5 additional patients has been reversed with prednisone.

DIE ROLLE DER NIERE BEIM REZENTEN DIABETES MELLITUS. (THE ROLE OF THE KIDNEY IN RECENT DIABETES MELLITUS).

Pavel, I.; Pieptea, M.R.; Mihalache, N.; Antonescu, E., and Tanasescu, N. *Medizinische* No. 1, Jan. 1959, p. 8; through Ciba Literature Review **4:** 41, 1959.

The part played by the kidney in recent cases of diabetes mellitus was investigated. The investigation of renal function can indicate whether the glycosuria is to be regarded as the sign of a general metabolic disorder (diabetes mellitus) or of renal dysfunction. Twenty adults who had had diabetes for less than two years were examined. The glomerular filtration rate was found to be about 30 per cent above normal. The tubular reabsorption of water reached the usual levels when fluid intake was normal, but was reduced following the water test. The tubular reabsorption of glucose was sometimes normal, and sometimes as much as 60 per cent below normal. In the opinion of the authors, that form of incipient diabetes mellitus in adults in which the tubular reabsorption of glucose is reduced is due primarily to a disturbance of the hypothalamopituitary system. This view is further supported by the fact that in these patients the disease has run a benign course for a long time—a typical feature of diabetes mellitus caused by pituitary dysfunction. It is possible that in these cases the blood sugar concentration, which is for some considerable time only relatively slightly elevated, may prevent early exhaustion of the endocrine pancreas.

VISUAL IMPROVEMENT IN SENILE RETINOPATHY FOLLOWING LIPOTROPIC THERAPY.

Pickens, J. L. *J. Arkansas M. Soc.* **55:** 341 (Feb.) 1959.

Lipotriad (a combination of choline, inositol and methionine with vitamin B complex factors and vitamin B_{12}) over a four-year period was administered three times daily for several months to each of 376 patients with uncomplicated senile retinopathy. All except 3 patients were between the ages of 50 and 90 years, and 75 per cent of them were between 60 and 80 years of age. Results are reported on 340 eyes that could be observed during several months' therapy. Central visual efficiency was graded in percentage values according to the system of the Council on Industrial Health of the American Medical Association (1955), using 20/20 as 100 per cent. An increase in central visual efficiency occurred in 59 per cent of the 340 eyes. The increase in efficiency was between 5 and 20 per cent in 181 of the 202 eyes

showing improvement. No change occurred (no improvement, but no further loss in visual acuity) in 27 per cent of the eyes. Progressive retinal degeneration occurred in 14 per cent. In addition to improvement in vision, improvement in appetite and in the patients' general health and vigor was seen. Lipotriad is helpful in uncomplicated senile retinopathy and offers a sound nutritional approach to the control of loss of central vision in elderly persons.

ETUDE ANATOMIQUE ET FONCTIONNELLE DU PANCRÉAS EXOCRINE DU VIEILLARD. (ANATOMICAL AND FUNCTIONAL STUDY OF THE EXOCRINE PANCREAS IN ELDERLY PATIENTS).

Puech, A.; Pagès, A., and Hertault, J. *Montpellier med.* **51:** 557, 1957; through Excerpta Med. (Gerontol & Geriatrics) **2:** 5, 1959.

The senile pancreas is characterized anatomically by considerable sclerous alterations which increase with age until, especially in patients over 80 years of age, a veritable pancreatic cirrhosis has developed. Secondary and associated changes of the acini and excretory ducts, and adipose invasion of the organ complete the histologic description of the "senile pancreas." Functional exploration of the pancreas, at least by iodated oil, yields more precise results. Although on the whole lipase activity of the pancreas is slowed down in old age, there are gross individual differences, less according to age than according to the pathologic past history and the local, regional or general organic soil.

RESPONSE TO SEROTONIN AND ITS ANTAGONISTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND RELATED DISEASES.

Scherbel, A. L., and Harrison, J. W. *Angiology* **10:** 29 (Feb.) 1959.

Patients with rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, or acrosclerosis showed an exaggerated reactivity to the extravascular injection of serotonin. The response was manifested by pain, swelling, erythema and cyanosis which spread rapidly and persisted for prolonged periods. This reaction could be antagonized by the administration of 2-bromo-d-lysergic acid diethylamide or of Hydergine. Histamine alone by periarticular or intradermal injection caused itching, swelling and erythema. When it was combined with serotonin and given by periarticular injection, the exaggerated reaction that followed lasted longer than that due to the administration of either amine alone. Injected in a similar manner, epinephrine and norepinephrine caused local pallor and venous constriction. Acetylcholine caused only mild transient, local erythema.

AKINESIA IN PARKINSON'S DISEASE.

Schwab, R. S.; England, A. C., and Peterson, E. *Neurology* **9:** 65 (Jan.) 1959.

Akinesia is the term chosen to describe the motor impairment resembling fatigue in patients with Parkinson's disease. An ergograph was used to measure voluntary muscle activity and that following electrical stimulation. Objectively, akinesia includes: a reduction in level of most motor tasks, extreme fall-off from reduced to lower levels, inability to complete actions, difficulty in releasing active muscles, extreme loss of ability to start or sustain an act when a second one must be performed, loss of many cooperative or associated motor acts producing extreme mechanical inefficiency, ability to reach normal levels briefly under sudden motivation, a voluntary ergogram that is one-half to one-tenth of the near normal electronic ergogram. Studies of the correlation of akinesia with clinical features of Parkinson's disease in 50 patients showed no relation to tremor, but a relation to abnormal electrocardiograms, cortical atrophy by air studies, sensitivity to belladonna and sedative drugs, and loss of intellectual ability, alertness and motivational drive. Most of the medications effective against tremor and rigidity do not relieve akinesia. In fact, it is made worse by the usual medications and sedatives and by neurosurgical intervention. Analeptics and physiotherapy may help slightly. One of the best aids is an understanding and energetic wife or nurse.

LA RÉSERPINE EN CARDIOLOGIE EN DEHORS DE L'HYPERTENSION. (RESERPINE IN CARDIAC DISEASE WITHOUT HYPERTENSION).

Stéphan, E. *Rev. méd. Moyen Orient* **15:** 195, 1958; through Ciba Literature Review **4:** 50, 1959.

The results obtained in more than 600 patients with Serpasil are described. The drug is usually administered orally in initial doses of 0.25 to 0.5 mg. and the dosage gradually increased when necessary. Intravenous injection (using 1 mg.) is indicated in emergencies. Particularly good results may be expected with Serpasil in sinus tachycardia of varying origin, paroxysmal tachycardia, and auricular flutter. Patients with angina pectoris and tachycardia often showed astonishing improvement. In cases of myocardial infarction, it is advisable to prescribe Serpasil beginning on the eighth or ninth day, in order to eliminate tachycardia. Reserpine is also frequently of great value in cardiac defects and active rheumatic cardiac processes. In the presence of cardiac insufficiency, irrespective of its origin, Serpasil is useful as an adjuvant to treatment with cardiac glycosides. According to Stéphan, Serpasil can be relied upon to bring the heart rate down to 60 or 55. It apparently is possible with Serpasil to break through the vicious cycle of tachycardia and heart disease which probably is responsible for the cardiopathy becoming chronic and progressively worse. Serpasil may, therefore, be regarded as a drug with a physiologic action in cardiotherapy.

AORTITIS AND AORTIC REGURGITATION ASSOCIATED WITH RHEUMATOID SPONDYLITIS.

Toone, E. C., Jr.; Pierce, E. L., and Hennigar, G. R. *Am. J. Med.* **26:** 255 (Feb.) 1959.

Aortitis and aortic insufficiency were found in 8 patients during the course of examinations made in 265 patients with rheumatoid spondylitis. There was no evidence of syphilis in any of the 8 patients, a questionable history of rheumatic fever in 1, and evidence of peripheral rheumatoid arthritis in 5. Rheumatoid spondylitis was diagnosed on the basis of typical roentgen changes in the sacroiliac joints, and aortic insufficiency by a diastolic murmur heard over the aortic valve area and along the left sternal border by at least 2 observers. In addition to the diastolic murmur of aortic insufficiency and the wide pulse pressure, the following cardiac manifestations were noted: left ventricular enlargement, first degree A-V block, left bundle-branch block, Wenckebach's phenomenon, substernal pain suggestive of coronary insufficiency, pericarditis and congestive heart failure. Pathologic examination showed the following types of lesions in the 2 cases: 1) dilated incompetent aortic valves; 2) shortened, thickened aortic valve cusps with rounded margins but with no evidence of fusion; 3) a dilated aorta with the intima wrinkled, thickened, and covered with pale noncalcified plaques; 4) patchy destruction of the elastica of the media with replacement by fibrous tissue; 5) endarteritis obliterans of the vasa vasorum of the tunica externa associated with perivascular infiltration and fibrosis; and 6) absence of any significant damage to the other valves of the heart. These changes were most prominent at the base of the aortic valve cusps and the ascending portion of the aorta. In 1 case the gross changes extended to the level of the renal arteries. The findings in these 2 cases and a review of those previously reported indicate a specific relation between rheumatoid spondylitis and this type of aortitis. (From authors' summary.)

LA CORTICOTHÉRAPIE INTRA-ARTÉRIELLE DANS LE TRAITEMENT DES ARTÉRITES. (INTRA-ARTERIAL CORTICOSTEROID THERAPY IN THE TREATMENT OF ARTERITIS)

Wertheimer, P.; Plauchu, M.; Mounier-Kuhn, A.; Dalmais, J., and Rondelet, J. *Lyon méd.* **34:** 203, 1958; through Ciba Literature Review **4:** 53, 1959.

The intra-arterial injection of water-soluble hydrocortisone, prednisone, or prednisolone derivatives elicited a partial response in various cases of arteritis, such as diabetic arteritis,

thrombo-angiitis, and degenerative arteritis in old people which was often combined with intermittent caludication. Each patient received six to twelve injections into the femoral artery, the injections being given daily or every other day. The dose was 25 mg. initially, often increased to 50 mg. towards the end of the course of treatment. The results were good or very good in 7 cases and moderately good in 2. Claudication was also considerably improved in 2 patients. Pain responded well to this therapy, subsiding or disappearing a few minutes after the injection, regardless of whether the hormone was combined with procaine or not. The analgesic effect lasted from twenty-four to thirty hours, the effect being greatest following the first few injections and then gradually decreasing. As a rule, the gangrenous process became inexorably worse. It should be remembered, however, that these were severe, advanced cases. The hormones seemed to have both a local and a systemic effect, but the mode of action still is unknown.

News and Notices

COURSE IN REHABILITATION CARE OF THE CHRONICALLY ILL PATIENT

A one-week course for physicians, devoted to the rehabilitation care of the chronically ill patient, will be held *November 16–20, 1959* under the auspices of the Department of Physical Medicine and Rehabilitation, New York Medical College-Metropolitan Hospital Center. The course will offer a review of the principles and techniques in the medical care of the chronically ill to meet the needs of the clinician, medical administrator and Public Health physician. Course content will include: Physiology and Pathology of Chronic Diseases, Nutrition and Dental Care, Management of Bedridden and Incontinent Patients, Home Care Programming, Community Needs and Resources, Public Health Aspects, Self-Care Activities, Prosthetic Devices and Psychological and Social Aspects.

The tuition fee is $100.00. Traineeships for tuition, maintenance and travel are available through funds provided by the U. S. Office of Vocational Rehabilitation. Applications for the course and traineeships can be obtained directly from Dr. Jerome S. Tobis, Chairman, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York 29, N. Y.

ANNUAL MEETING OF THE FLORIDA DIABETES ASSOCIATION

The Florida Diabetes Association will hold its Annual Meeting on Thursday and Friday, *October 29 and 30, 1959*, at the Balmoral Hotel, Bal Harbour, Miami Beach, Florida.

The following out-of-state speakers are included on the program:

Dr. Francis D. W. Lukens, Professor of Medicine, University of Pennsylvania.

Dr. Jerome W. Conn, Professor of Medicine, University of Michigan.

Dr. Nicholas P. Christy, Columbia University and Presbyterian Hospital.

All members are urged to attend this important meeting.

Moris B. Seltzer, M.D., Secretary-Treasurer,
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